THE VEIN BOOK

EDITED BY

JOHN J. BERGAN

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John J. Bergan

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NEW YORK • OXFORD • PARIS • SAN DIEGO
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Academic Press is an imprint of Elsevier

Elsevier Academic Press

30 Corporate Drive, Suite 400, Burlington, MA 01803, USA
525 B Street, Suite 1900, San Diego, California 92101-4495, USA
84 Theobald's Road, London WC1X 8RR, UK

This book is printed on acid-free paper. ♾

Library of Congress Cataloging-in-Publication Data

The vein book / editor, John J. Bergan.
p. ; cm.
Includes bibliographical references.
ISBN-13: 978-0-12-369515-4 (hardcover : alk. paper)
ISBN-10: 0-12-369515-5 (hardcover : alk. paper)
1. Veins–Diseases. I. Bergan, John J., 1927– .
[DNLM: 1. Vascular Diseases. 2. Veins. WG 600 V4265 2007]
RC695.V438 2007
616.1′4—dc22
2006026762

British Library Cataloguing in Publication Data

A catalogue record for this book is available from the British Library

ISBN 13: 978-0-12-369515-4
ISBN 10: 0-12-369515-5

For all information on all Elsevier Academic Press publications
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Printed in the United States of America
07 08 09 10 9 8 7 6 5 4 3 2 1

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Preface

Over the last decade, the art and science of surgery have changed dramatically. At this time, we in surgery are moving from open surgery to minimally invasive interventions. We have moved in some instances from operative procedures to catheter-based or endoscopic manipulations. Where data are available, we have moved from experience-driven dogma, through retrospective analysis of experience, to evidence-based medicine from prospective randomized trials. Almost all these changes can and should be viewed as good omens for our patients and for our ability and security in practicing surgery.

Some areas of surgery have been more resistant to change and have proven to be difficult to change. Such is the story of venous disorders. Up until quite recently, it seemed that the only solution that we could provide in evaluating venous disorders of the lower extremities was the dogma handed down by our teachers. Now, there has been extensive scientific activity working on solutions to these stubborn problems. The current volume, edited and shepherded by the eminently qualified Dr. John Bergan, both catalogues the significant advances in this arena and offers practitioners an up-to-date guide for treating patients. It is a most welcome effort, a superb product, and it places a scientific stake in the ground for the modern diagnosis and treatment of venous disorders. You will enjoy this volume, and you will refer to it frequently when treating the unfortunate individuals disabled by venous diseases.

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Prologue

Although it generally is acknowledged that venous disorders have an enormous socio-economic impact, diagnosis and treatment of such conditions have suffered from a lack of interest and support, especially in academic centers. All specialities have considered phlebology as a kind of unimportant appendix to their main discipline. So this subspecialty has gained the reputation of a Cinderella in clinical medicine.

As a matter of fact, venous disorders are much more complex than, for instance, peripheral arterial occlusive diseases. At the beginning of this new millennium there are encouraging signs that the period of stagnation has ended.

The Vein Book gives impressive testimony documenting the rapid ascent of the subject of venous disorders into the world of science. The transition from dogma of the nineteenth and twentieth century to evidence-based medicine and medicine-based evidence exemplifies this. Future developments can already be seen, and the way ahead looks very promising.

Fascinating new insights in the fields of basic science will certainly stimulate more clinical research. The new tools of noninvasive diagnostic instrumentation, such as the duplex Doppler, have opened our eyes to an improved anatomic and functional understanding of venous pathology. Nowadays this has become the basis for rational therapeutic decisions and for assessing the outcome after treatment.

New therapeutic options for treating varicose veins have been developed, which are less invasive and are at least as effective as traditional surgical methods. Based on the growing experience with such procedures and on the results of comparative studies, the indications for surgery of varicose veins have changed and will certainly change in the near future.

Abolishing superficial reflux and also advanced reconstructive surgical procedures on the deep veins may soon yield excellent results, especially in severe forms of chronic venous insufficiency. These conditions, especially venous ulcerations, have been considered until now to be chronic, incurable lesions.

Venous disorders frequently start with acute thrombosis. This is but one feature of a complex thromboembolic disease process that provides appealing links with other fields of medicine. An example is the fascinating area of coagulation disorders. A major part of this volume, *The Vein Book*, is written by some of the most internationally recognized experts in thrombosis research who provide genuine insights into this important subject.

The future of phlebology has already arrived, and *The Vein Book* is destined to be a part of it.

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Professor at the Medical University
and Honorary President of the IUP.
Vienna, November 2005

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Introduction

Venous disorders are important. They range in severity from trivial telangiectasias to death-dealing pulmonary embolization. Their impact on disability is enormous. Their cost to the economic system in Western countries is almost incalculable. This volume intends to bring under a single hardcover the major facets that have changed the face of diagnosis and treatment of venous disorders during the last quarter century.

Much of the activity in diagnosis and treatment of venous disorders actually has been in investigations toward causation. These are well represented in this volume, where the molecular basis of venous insufficiency is discussed as well as in the inappropriate activity of leukocytes and how this impacts on venous function. This is discussed further in the chapters on physiologic testing of venous disorders. All of this, of course, is based on the anatomical findings and the newly uncovered pathologic anatomy revealed by ultrasound testing.

Classification of venous dysfunction has undergone some revisions and has helped in making treatment of venous insufficiency more of a science. The fundamental basis for all treatment in venous disorders is compression therapy, and this is thoroughly discussed in this volume by a preeminent authority in this field.

After 1970, the vascular laboratory became dominant in the study of patients with arterial diseases. After 1980, use of the Doppler and its marriage to pulsed Doppler systems made venous diagnosis more accurate. Since 1985, duplex scanning has emerged as the main direct test for diseases of the veins. The ultrasound applications are seen throughout this volume. These are mentioned many times in those chapters that deal with primary venous insufficiency.

In treating venous insufficiency, compression is fundamental and this is well discussed, as is sclerotherapy, which is described in a number of chapters encompassing the sclerosants themselves, their applications, and the all important complications of sclerotherapy.

As treatment of varicose veins has changed from traumatic surgery to minimal invasion, the new modalities command attention. These include modifications of surgery, radiofrequency closure of the saphenous vein, use of the laser in obliteration of the saphenous vein, and the use of foam as a substitute for all three modalities. No book of this magnitude would be complete without a description of the surgical stripping of the saphenous vein, even though many phlebologists believe that to be obsolete. Part of the reasons for the downturn in interest in surgery is the phenomenon of neovascularization, which appears to be the consequence of a clean groin dissection, and that is exceedingly well described in a chapter on that subject.

Venous thromboembolic disease is an exceedingly important venous subject although it is quite separate in its thinking from the general subject of venous insufficiency. A complete coverage of this subject extends from diagnosis through various forms of treatment and must contain a thorough discussion of prevention as well as treatment.

Finally, the post-thrombotic state of chronic venous insufficiency occupies much time and effort because it is essentially incurable. Aspects of its care run the full gamut from simple compression through surgery, venous reconstruction, and foam sclerotherapy to the futuristic subject of synthetic and artificial valves. There is much to be done in improving the care of this condition.

All these subjects and more are the content of this volume. The authors of each chapter and section join me in the hope that you will enjoy application of the knowledge as much as we have enjoyed bringing it to you.

John Bergan, M.D.
La Jolla, CA, USA
November 2005

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CHAPTER

1

Historical Introduction

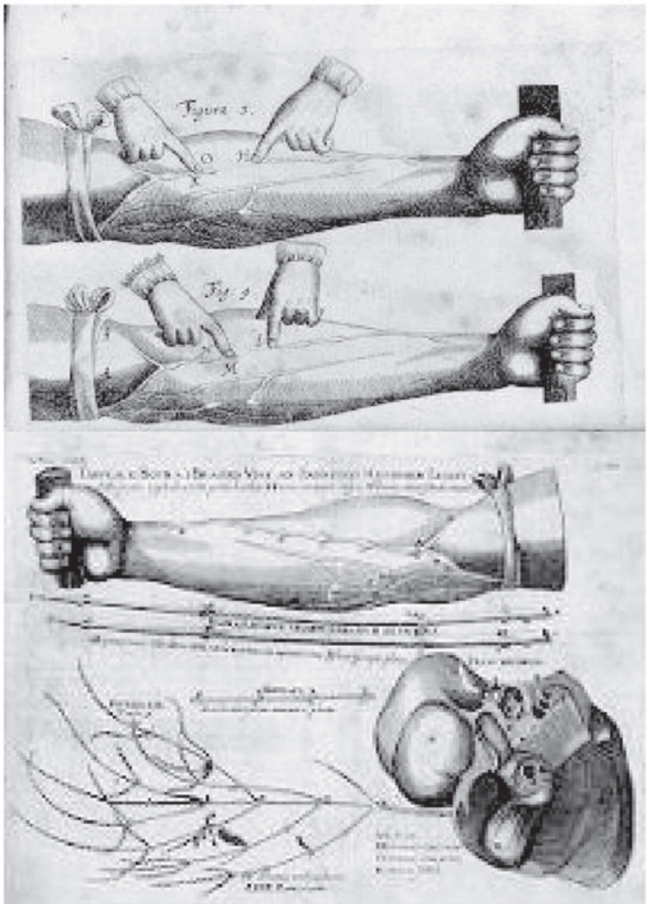
ALBERTO CAGGIATI and CLAUDIO ALLEGRA

Since the fifth century BC, the heart has been regarded as the center of the vascular system (Empedocles of Agrigentum; 500–430 BC). In the great Epic of India, "Mahabharata," it was stated that "all veins proceed from the heart, upwards, downwards and sideways and convey the essences of food to all parts of the body." The Chinese Wang Shu So reported in his Mei ching, that "the heart regulates all the blood in the body . . . The blood current flows continuously in a circle and never stops . . ." Herasistratus (310–250 BC) was so close to the discovery of the circulation to guess the existence of capillaries: ". . . the blood passes from the veins into arteries thorough 'anastomoses,' small inter-communicating vessels . . ."

These correct theories were darkened by Hippocratic dogma for centuries. Hippocrates of Cos, the "father of the Medicine" (460–377 BC) affirmed in "De Nutritione" that the liver is the "root" of all veins and that the veins alone contain blood destined for the body's nourishment. Arteries would contain an elastic ethereal fluid, the "spirit of life." This wrong convincement, based upon the Pythagorean doctrine of the four humors (blood, phlegm, yellow bile, and black bile), remained the basis for medical practice for more than 2000 years!

As irrational as this theory seems to us today, more than three centuries (1316–1661) passed until it was abolished. Many authors confuted Hippocratic theories, allowing, and sometimes anticipating, Harvey's discovery. In 1316, Mondino de Luzzi furnished a rudimental but exact description of the circulatory system that was omitted by all subsequent authors: ". . . *Postea vero versus pulmonem est aliud orificium venae arterialis, quae portat sanguinem ad pulmonem a corde; quia cum pulmo deserviat cordi secundum modum dictum, ut ei recompenset, cor ei transmittit sanguinem per hanc venam, quae vocatur vena arterialis; est vena, quia portat sanguinem, et arterialis, quia habet duas tunicas; et habet duas tunicas, primo quia vadit ad membrum quod existit in continuo motu, et secundo quia portat sanguinem valde subtilem et cholericum* . . ." The same occurred to the Spanish Ludovicus Vassaeus and Miguel Servetus. The anatomy of the cardiovascular system was so well depicted by Vassaeus (De Anatomen Corporis Humani tabulae quator, 1544) that Marie Jean Pierre Florens affirmed that he ". . . described the blood circulation a century before William Harvey . . ." In 1546, the anti-Arabist theologician and physician Servetus exactly described the pulmonary circulation: ". . . the blood enters the lungs by the way of the pulmonary artery in greater quantities than necessary for their nutrition, mixes with the pneuma and returns by way the pulmonary veins . . ." Servetus' discovery did not diffuse between contemporary physicians, probably because it was reported in a theological book. Servetus' theories were so innovative that he was accused of heresy by Calvinists and burned. Andrea Cesalpino, Professor of Medicine at Rome, first identified the function of the valves (. . . certain membranes placed at the openings of the vessels prevent the blood from returning . . .) and the centripetal direction of the flow in the veins (1571). He also supposed the existence of "*vasa in capillamenta resoluta*" (capillaries) and affirmed that in the lung, the blood ". . . is distributed into fine branches and comes in contact with the air . . ." (1583). Finally, he coined the term "circulation." According to important historians like Florens, Richet, and Castiglioni, Cesalpino's groundwork determined the Harvey's revolution.

In 1628, William Harvey explained in his *De Motu Cordis* the theory of the blood circulation (see Figure 1.1). However, the discovery of the circulation cannot be considered



A

B

FIGURE 1.1 A) The famous illustration used by Harvey in his *De motu cordis* (1661) showing the direction of flow into the veins and B) the plate published 60 years before by Hyeronimus Fabricius of Acquapendente (1603).

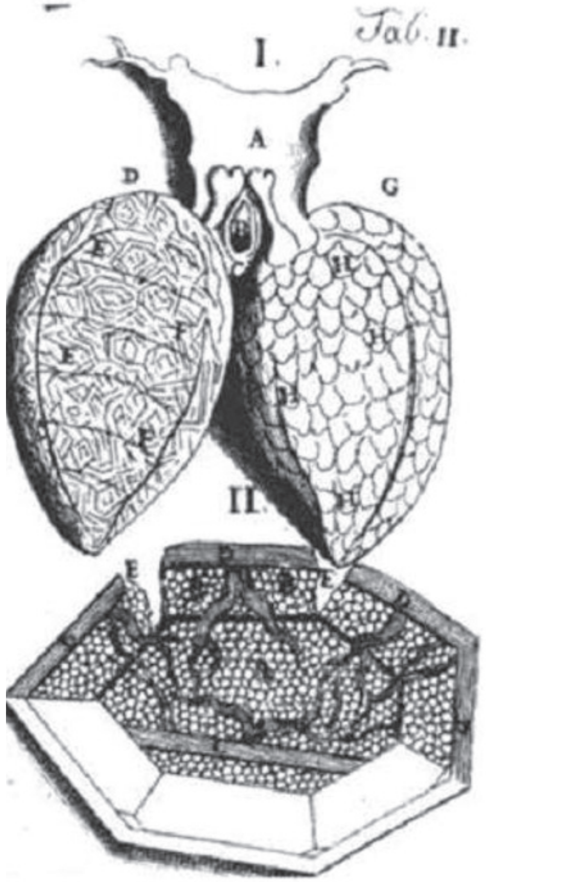


FIGURE 1.2 The original Malpighi's representation of the lung capillary bed (*De Pulmonibus*, 1661).

complete until 1661, when Marcello Malpighi demonstrated by microscopy the existence of the capillaries in his *De Pulmonibus* (see Figure 1.2).

VENOUS ANATOMY

The first systematic description of the venous system was given by André Vesale (alias Vesalius) in *De humanis corporis fabrica* (1543). Vesalius' venous anatomy was almost complete (see Figure 1.3) containing some omissions, like venous valves and perforating veins. In addition, Vesalius furnished a good description of the structure of the venous wall. He differentiated the internal coat of the veins in two layers. The internal one contained contractile fibers, though "dissimilar from those of skeletal muscles, arranged, from within outwards, circularly, obliquely and longitudinally." The outer coat was formed by a loose network borrowed from surrounding structures.

VESALIUS'S OMISSION I: VENOUS VALVES

Giovanni Battista Canano from Ferrara, was the first to describe venous valves in 1540 ("*ostiola sive opercula*"), in the renal, azygos, and external iliac veins. According to Franck Cockett, ". . . he identified correctly the function of the valves, i.e., to avoid blood reflux . . ." Further sporadical descriptions of venous valves were given by the Spanish anatomist Ludovicus Vassaeus (1544) and, one year later, by Charles Estienne (apophyses membranarum). Valves in the veins of the lower limbs first were reported by Sylvius Ambianus in 1555, and their first illustrations appeared in the Salomon Alberti's *De valvulis membraneis vasorum* (1585). Finally, Hyeronimus Fabricius of Acquapendente published in 1603 an exhaustive description of the valves of the veins with magnificent figures (see Figure 1.4), which were used by his pupil Harvey to demonstrate the direction of flow (see Figure 1.1). Four centuries passed before it was demonstrated that venous valves do not only steer blood return and prevent reflux; according to Lurie et al., they also act as a venous flow modulator.[1]

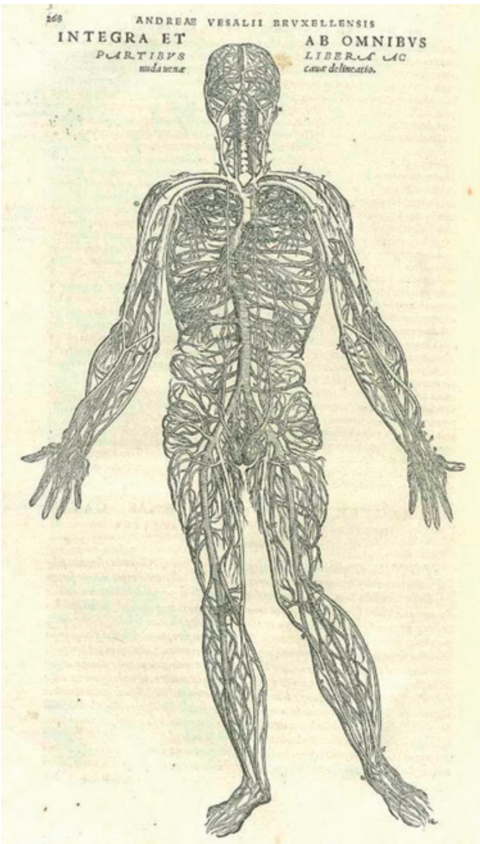


FIGURE 1.3 The Venous System according to Vesalius (1545).

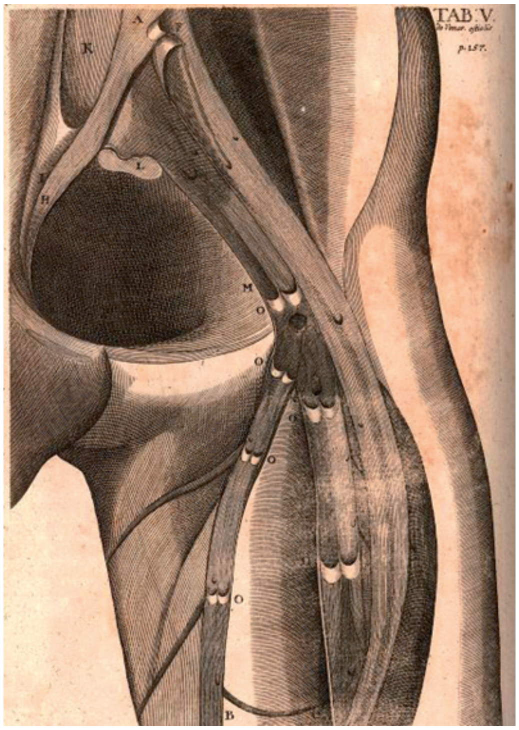


FIGURE 1.4 The Sapheno-Femoral Junction according to Fabricius (1603).

VESALIUS'S OMISSION II: PERFORATING VEINS

The second Vesalius's gap was filled at the beginning of the nineteenth century (1803), when the anatomist Justus Christian Von Loder represented exactly the more important perforating veins of the human body (see Figure 1.5). Von Loder omitted a description of their function; that was clarified only in 1855 when Aristide August Verneuil described the presence of valves within perforating veins and the direction of blood flow in them.

THE RETURN OF THE VENOUS BLOOD

The mechanisms allowing blood to flow centripetally along the veins were described more than two hundreds years ago (see Table 1.1). The "*vis a tergo*" was described in 1670 by Richard Lower: ". . . the return of the venous blood is the result of the impulse given to the arterial blood . . ." Furthermore, Lower acknowledged an important role to the "*venarum tono*" in venous return, and described the effects of the muscular pumping. Antonio Valsalva,

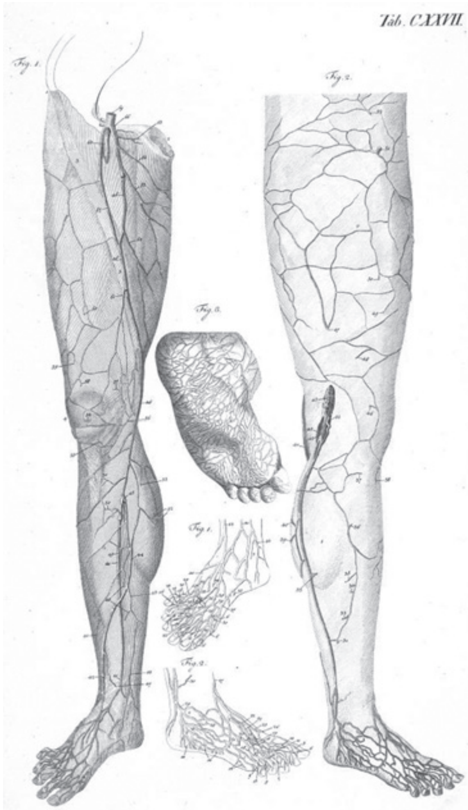


FIGURE 1.5 The first representation of perforating veins in Von Loder's *Anatomische Tafeln* (1803).

TABLE 1.1 Mechanisms of Venous Propulsion

1670	Richard Lower	Propulsive *Vis a tergo*
1670	Richard Lower	Muscle pump
1670	Richard Lower	Tone of the venous wall
1710	Antonio Valsalva	Aspirative *Vis a fronte*
1728	Giovanni Lancisi	Contraction of the venous wall
1793	John Hunter	Pulsation of neighboring arteries

pupil of Malpighi, described in 1710 the aspiratory forces that enhance venous return to the heart: the "*vis a fronte*" due to the rhythmic respiratory changes of thoraco-abdominal pressure. In 1728, Giovanni Lancisi demonstrated experimentally the spontaneous rhythmical contraction of larger veins. Finally, John Hunter suggested in 1793 that the pulsation of arteries assists the blood return in certain veins. J.F. Palmer, the editor of the posthumous Hunterian *Of the Vascular System* (1837), added a footnote: ". . . especially when a common sheath exists . . ."

ETIOLOGY AND PATHOGENESIS OF VARICOSE VEINS

Hippocrates was the first to deal with the pathogenesis and epidemiology of varicose disease when he affirmed that varicose veins were more frequent in Scythians due to the prolonged time spent on the horseback with the legs hanging down. In 1514, Marianus Sanctus noted that varicose veins were more frequent after pregnancy and in longtime standing peoples (". . . standing too much before kings . . ."). In 1545, Ambroise Paré related varicose veins to pregnancy and long travelling and affirmed that they are more frequent in melancholic subjects. Ten years later, Jean Fernel (1554), Professor of Medicine at Paris, stated that varicose veins can develop after an effort or a trauma: ". . . the varix comes also from a blow (?), from a contusion, from an effort . . ." Virchow (1846) was the first to point out the hereditary tendency to varicose veins. Finally, the rare syndrome due to congenital absence of venous valves was first reported by Josephus Luke in 1941.

The first to attribute the onset of varicose veins to valvular incompetence was Hyeronimus Fabricius (1603). The parietal theory first was promulgated by Richard Lower, who in 1670 affirmed that a "*relaxatio venarum tono*" (wall muscular looseness) is the cause of venous stasis and dilation. Pierre Dionis credited in 1707 an important role to mechanical compression of large trunks in the development of varicose veins, whereas Jean Louis Petit (1774), the eminent French surgeon, reported their possible occurrence during obstruction of proximal veins. According to these two authors, the clinical syndromes due to compression of the left common iliac vein were described by the Canadian McMurrich in 1906, and of the popliteal vein by Rich and Hughes in 1967. Al Sadr described in 1950 the compression of the left renal vein by the aorta and the superior mesenteric artery. Paul Briquet was the first to affirm in 1824 that varicose veins are due to abnormal flow coming from deep veins via the perforators. In 1944, Malan described the occurrence of varicose veins in limbs with abnormal arteriovenous connections. The theory of a subclinical parietal phlogosis inducing venous valve disruption has been proposed only recently by Ono, Bergan, and Schmid-Schonbein.[2]

VENOUS THROMBOSIS

In 1544 the Spanish anatomist Ludovicus Vassaeus first identified the "vascular dessication" described by Hippocratic medicine with the phenomena of "coagulation," that is, loss of the liquid state of the blood. One year later, Paré first described superficial phlebitis (". . . a swollen vein, with jelly blood, spontaneously painful . . ."). In 1793, John Hunter introduced the term *Phlebothrombosis* and affirmed that inflammation of the venous wall is always accompanied by the formation of a clot. Matthew Baillie (1793), in contrast to Hunter, considered flow deceleration the cause of thrombosis. Rudolf Virchow, the greatest pathologist of all times, defined in 1846 the famous triad of conditions essential for development of thrombosis: slowing of flow or its cessation, excess of circulating thrombogenic factors, and disruption of the endothelial lining. Only one century later (1946), MacFarlane and Biggs described the "cascade" mechanism for coagulation.

The "white swelling" of the lower limb or *phlegmasia alba dolens* was accounted for by Charles White in 1784. In 1857, Jean Baptiste Cruveilhier described the "phlébite bleue" (*phlegmasia coerulea dolens*) and affirmed it is due to the thrombosis of all the veins with patency of the arteries (see Figures 1.6 and 1.7). Sir James Paget investigated the pathogenesis of phlebitis and described in 1866 a great number of possible causes: traumatic phlebitis; distension phlebitis; phlebitis occurring in exhaustion or during either acute or chronic disease; phlebitis due to extension of inflammation from an ulcer; idiopathic, puerperal, and pyemial phlebitis, and finally, phlebitis occurring in varicose limbs. A clear nosologic discrimination between phlebothrombosis and thrombophlebitis was finally indicated by Ochsner and De Bakey in 1939. The possible occurrence of venous thrombosis of the leg due to prolonged sitting was first described by John Homans (1954). Incorrectly, the association of prolonged sitting and venous thrombosis was then limited to air travel and assumed the name of "Economy Class Syndrome."

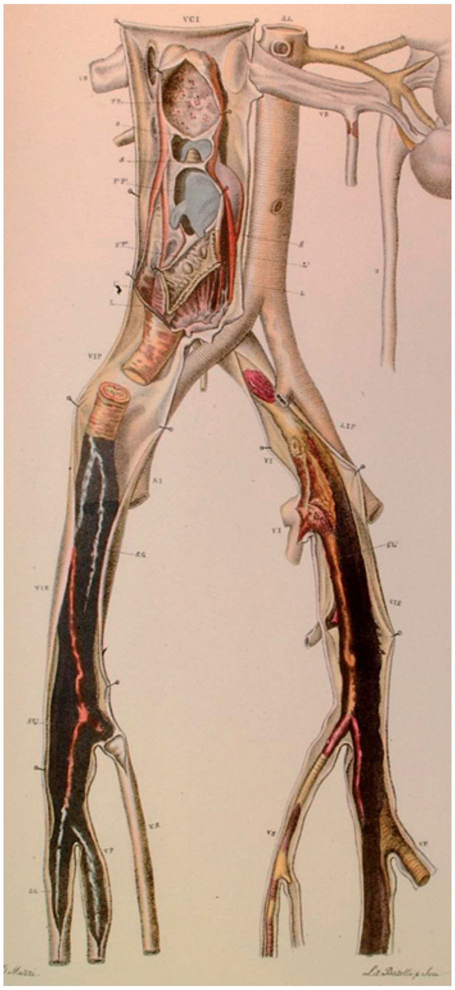


FIGURE 1.6 Ileocaval thrombosis (Cruveilhier, 1857).

FIGURE 1.7 Post-thrombotic varicose veins (Cruveilhier, 1857).

DIAGNOSIS OF VENOUS DISORDERS

Clinical Semiotics

Clinical semiotics started in 1806 when the Swiss surgeon Tommaso Rima described a simple test for the diagnosis of saphenous reflux. In 1846, Sir Benjamin Brodie described a method of testing for incompetent valves by constriction of the limb and palpation. These two tests were reproposed by Friedrich Trendelenburg in 1890. In 1896, Georg Perthes of Bonn described the famous test to verify the patency of the deep veins. Finally, in 1938, John Homans described a test for detection of deep venous obstruction based upon foot dorsiflexion. Surprisingly, these tests and maneuvers still appear in modern texts of vascular medicine and venous surgery.

Phlebography

The history of phlebography started in 1923, when Berberich and Hirsch described the technique to demonstrate the venous system in living humans by infusion of strontium bromide. One year later, Sicard and Forestier performed the first phlebography in humans using Lipiodol. In 1929, McPheeters and Rice performed the first dynamic varicography and described the movement of blood in the varicose veins. Further developments were due to Ratschow (who in 1930 introduced water soluble contrast media for angiography), Dos Santos (who demonstrated in 1938 the utility of direct ascending contrast venography to detect deep venous thrombosis), and Farinas (who performed the first pelvic venography in 1947). Intraosseus phlebography was then proposed by Schobinger in 1960 and refined by Lea Thomas in 1970. Finally, Dow described in 1973 the technique to perform retrograde phlebography.

Traditional venography is even less used in daily practice due to the achievement of duplex sonography. However, radiologic venous imaging recently improved due to the introduction of computed tomography (CT) and magnetic resonance (MR) techniques. CT was introduced in 1980 to demonstrate venous thrombosis by Zerhouni. Multislice CT, proposed first in 1994 by Stehling to evaluate the venous

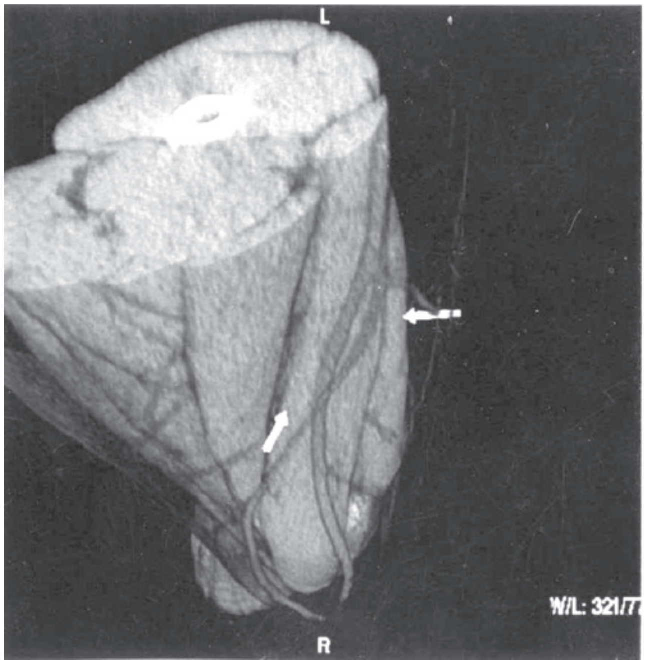


FIGURE 1.8 The first contrastless 3D venography by multislice CT (Caggiati, 1999).

bed of the lower limb, also is indicated for the contemporary evaluation of the pulmonary vessels. More recently, multislice CT has been proposed to obtain 3D images (see Figure 1.8) of superficial veins[3] with special reference to the preoperative evaluation of varicose limbs.[4] MR was introduced in the field of the diagnosis of DVT in 1986 by Erdman. MR venous imaging improved since 2001, when the group of Jorge Debatin proposed the technique called "low-dose, direct-contrast-injection 3D MR venography."[5]

Ultrasonic Venous Flow Evaluation and Imaging

The history of ultrasounds in venous medicine started in 1961 when Stegall and Rushmer described the first Doppler instrument and the basis for its practical use. A refinement of the Doppler techniques for venous investigations was made in 1967 by Sigel and coworkers. One year later, fundamentals of Doppler investigation of deep venous thrombosis were furnished separately by Evans and Cockett, and Sumner and Strandness. The technique to evaluate valvular competence was deeply investigated in 1970 by Folse and Alexander.

The history of venous echotomography started in 1976, when Day focused the possible role of B-mode imaging of venous thrombi. Duplex scanning was proposed for the diagnosis of venous disorders in 1986 by the group of Szendro, Nicolaides, Myers, Malouf et al.[6] and by that of Luizy, Franceschi, and Franco.[7]

TABLE 1.2 Proposals for Evaluation of Venous Disorders

1948	Pollack and Wood	Dynamic measurement of venous pressure
1953	Whitney	Impedance plethysmography
1960	Hobbs and Davies	Detection of thrombi by radioactive iodium
1968	Dahn	Strain gauge plethysmography
1969	Webber	Detection of thrombi by radioactive technetium
1971	Rosenthal	Radionuclide venography
1973	Norgren and Thulesius	Foot volumetry
1973	Cranley	Phlebo-rheography
1979	Abramovitz	Photo-plethysmography
1987	Van Rijn	Air plethysmography

Other Diagnostic Techniques

Other techniques have been proposed in the daily clinical evaluation of venous disorders (see Table 1.2).

COMPRESSION THERAPY

It was well known since ancient civilizations that compression is the main therapeutic option for the conservative management of limbs afflicted with chronic venous insufficiency. Henry de Mondeville (1260–1320) affirmed that ". . . compression expels bad humors that infiltrate legs and ulcers . . ." The effectiveness of compression was explained in 1824 by Sir Astley Paston Cooper, who affirmed that it allows the venous valves to regain their competence. Clinical and hemodynamic effects of compression and bandages in the field of treatment of any form of venous insufficiency and of phlebitis are still deeply investigated.[8]

Techniques of bandaging changed poorly along the course of the centuries. Since the fifth century BC, Hippocrates meticulously described how to perform leg bandages and how to obtain an eccentric compression by placing a sponge under the bandage. Giovanni Michele Savonarola (grandfather of the theologician Girolamo Savonarola) recommended in 1440 to extend the application of bandages to the thigh. Bell (1778) proposed to associate bandage to bed rest, whereas Underwood (1787), to deambulation. In 1849, Thomas Hunt warned that bandages must be done only by surgeons.

The use of compressive bandaging was extended to treatment of acute phlebitis in 1826 by Alfred Armand Louis Marie Velpeau, and associated with immediate mobilization by Einrich Fisher in 1910 in order to enhance its beneficial effects. Intermittent compression for the prevention of DVT and of its sequelae was proposed in 1971 by Sabri.

Materials for bandages varied greatly along centuries. Celsus used linen rollers, Galen preferred wool, as well as split and sewn bandages. Aetius put bandages in an

ear-of-corn shaped fashion. Fabricius introduced laced stockings made from dog's skin. At the end of the eighteenth century, dog skin was abandoned and laced stockings were made with linen. In 1783, Underwood first used an elastic bandage obtained with a Welsh flannel. At the same time (1797) Baynton introduced the homonymous bandage done with small plasters of pitch, resin, and lithargyre. Adhesive bandaging was introduced by Dickson Wright in 1830. Five years later, Muray and Claney described the first mechanical device for compression of the limb. Thanks to the introduction of rubber vulcanization in 1839 by Goodyear, elastic stockings were ideated and patented by William Brown in 1848. In 1878 Martin proposed to obtain elastic compression with rubber bandages. In 1896, Paul Gerson Unna combined local treatment with compression for treatment of venous ulcer by incorporating emollient compounds in a dressing that becomes increasingly rigid. The first seamless compression stocking is dated 1904, the first rubber-free in 1917. Ultra-thin rubber strings were introduced in the late 1930s.

In 1902, Hoffmeister described the principles of mercury compression obtained by placing the edematous limb in a reservoir with 50 ml of mercury. Pneumatic devices with laced chambers adaptable to any form of extremities were proposed in 1955 by Brush and, in the same year, Samson and Kirby described the first sequential pressure pneumatic device furnished with 14 compartments.

SCLEROTHERAPY

The beginning of sclerotherapy commonly is dated back to the invention of the the syringe by Pravaz (1831), and of the hypodermic needle by Rynd (1845). However, antique phlebologists could not wait for Rynd's and Pravaz's discoveries. In fact, the first endovenous treatment goes back to 1665 when Sigismond Johann Elsholz treated venous ulcers by irrigating them with intravenous injection of distilled water and essences from plants using a chicken bone as a needle and a bladder of pigeon as a syringe. Some authors credit Zolliker as the first to perform sclerotheraphy in 1682, by injecting acid into varicose veins. The rationale of sclerotherapy was furnished by Joseph Hodgson (1815) who noted first that "thrombosis extinguished varicose veins." In the second half of the eighteenth century, various substances were used (see Table 1.3), but adverse sequelae (local tissue necrosis, extravasation, pulmonary embolism, and scarring caused by poor technique and causticity of solutions) were so frequent and serious that, in 1894, at the Medical Congress of Lyon, sclerotherapy of varicose veins was firmly stopped. The adoption of safer sclerosants allowed, primarily in Europe, the renaissance of sclerotherapy at the beginning of the twentieth century.

Renaissance of sclerotheraphy was also due to safer techniques and to association to surgery. Tavel (1904) injected varicose veins after high ligation of the saphena. In order to avoid innumerable skin incisions, Benedetto Schiassi, from Bologna (1909), performed multiple injections of a combined iodine and potassium iodide immediately after saphenous interruption (see Figure 1.9). Linser (1916) suggested to use compression to reduce complication and to enhance the effects of the therapy. Ungher (1927) used a urethral catheter to perfuse varicose veins with sclerosing agents. Mc Ausland recommended in 1939 to empty the vein to be injected by elevating the leg and to bandage the leg after treatment.

TABLE 1.3 Some of the Sclerosant Agents Used

1840	Monteggio	Absolute alcohol
1853	Pravaz	Iron perchloride
1855	Desgranges	Iodotannin
1880	Negretti	Iron chloride
1894	**Medical Congress of Lyon: to stop sclerotheraphy!**	
1904	Tavel	Phenol + surgery
1909	Schiassi	Iodine and potassium iodide + surgery
1917	Kaush	Inverted sugar
1919	Sicard	Sodium salicilate
1926	Linser	Hypertonic saline
1930	Higgins and Kittel	Sodium morruate
1933	Jausion	Chromated glycerine
1946	Reiner	Sodium tetradecyl sulphate
1959	Imhoff and Sigg	Stabilized polyiodated ions
1966	Henschel and Eichenberg	Polidocanol

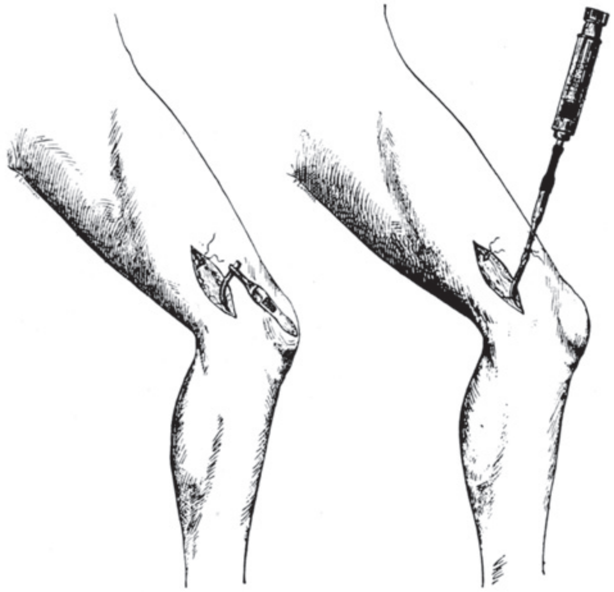


FIGURE 1.9 Schiassi's method to inject the Great Saphenous Vein at the same time of its interruption (1909).

Modern sclerotherapy developed in the 1960s. The tactics and the techniques to obtain even safer and more effective venous obliterations varied greatly between countries: the Swiss technique was proposed by Sigg; the French method by Tournay; Fegan popularized the so-called Irish technique and Hobbs the English method. These techniques differed with relation to: 1) position of the patient; 2) progression of injections (from larger to smaller veins, or vice versa); 3) sclerosant agents, their concentrations, and quantity; 4) modalities, duration, extension, and strength of compression; 5) size of the needle and modalities of injection.

In the last years, safety and accuracy of sclerotherapy greatly enhanced thanks to the introduction of real-time control of needle position and wall reaction by echotomography (echosclerosis, according to Schadeck). More recently, the effectiveness of sclerotherapy further improved thanks to the use of sclerosing foams, obtained by mixing slerosants with air (Tessari, Monfreux) or inert gas (Cabrera). However, the use of gas-sclerosant mixtures dates back to 1939 (Stuard Mc Ausland) and to 1944 (the "air-block technique" of Egmont James Orbach).

SURGERY OF SUPERFICIAL VEINS—THE DETRACTORS

In older civilizations, surgery of "serpent-shaped dilatations of lower limb veins" was advised to avoid dangerous hemorrhages and death (Papyrus of Ebers, 1550 BC). Only minimally invasive procedures were performed: ". . . the varix itself is to be punctured in many places, as circumstances may indicate . . ." in order to avoid that ". . . large ulcers be the consequence of the incisions . . ." (Hippocrates). This detracting convincement persisted along the centuries. As an example, Wiseman (1676) discommended surgery of varicose veins ". . . unless they were painful, formed a large tumour, ulcerated, or bled . . ." or when ". . . purging and bleeding, not once or twice, but often repeated, fail . . ."

SURGERY OF SUPERFICIAL VEINS—FORERUNNERS

First described by the Roman Celsus, hook extraction of the varicose vein, double ligation, and venectomy (or cautery) is the rough operation performed for centuries. Galenum used the hook to perform multiple ultra-short stripping of varicose veins. Great boost to varicose vein surgery come from the Byzantine physician Oribasius of Pergamum (325–405 AD), who devoted three chapters of his book to the treatment of varicose veins, operated by a special hook, called *cirsulce*. Many of his recommendations are still valid:

1. Remove the veins, because if only ligated, they can form new varices.
2. Shave and bathe the leg to be operated.
3. When the leg is still warm, the surgeon has to mark varicose veins with the patient standing.
4. Extirpate varicose veins of the leg first, then at the thigh.
5. Remove clots by external compression of the limb.

Further important contributions were from Paulus of Aegina (seventh century), who described the main anatomy of varicose veins and identified the great saphenous as their source. He isolated the varicose veins at the thigh by a longitudinal incision, and, after bloodletting, ligated them at both ends. The tied-off portion was excised or allowed to slough off later with the ligatures.

In Arab medicine, treatment of varicose veins was dominated by cautery. However, the Spanish El Zahrawi (Albucasis of Cordova) (936–1013) is credited by Anning as the first to use an external stripper. Williams of Saliceto advocated in his *Cyrurgia* (1476) the reintroduction of the knife into surgery and, a few decades later, Amboise Paré (1545) abandoned definitively external cauterization of varicose veins to reintroduce their ligation: ". . . the incision must be placed a little above the knee, where a varicose vein is usually found to develop . . . Ligature was needed for the purpose of cutting the channel and making a barrier against the blood and the humors contained within it which flow to varicose veins and fill any ulcer . . ." A similar technique was used by Sir Benjamin Collins Brodie (1816): ". . . after the skin over a varix was incised, the varix was divided with a curved bistoury and pressure was applied to prevent haemorrhage . . ." Lorenz Heister (1718) placed a wax thread transcutaneously around the distal end of a varicose vein. Eight to ten ounces of the grumous and viscid blood was allowed to escape as the varix was laid open longitudinally. The wound was then bandaged and compressed. This technique was reproposed one century later by Alfred Armand Louis Marie Velpeau (1826) who ". . . introduced a pin or needle through the skin, which is passed underneath the vein, and at right angles to it. A twisted suture is then applied round the two ends of the pin, so as to compress the vein sufficiently to produce its obliteration . . ." (see Figures 1.10 and 1.11). Max Schede in 1877 operated on varicose limbs by multiple ligature or venesections and percutaneous ligations. Delbet described in 1884 the reimplantation of the terminal portion of the great saphenous vein just below a healthy femoral valve. In the same year, Madelung proposed a complete excision of the great saphenous vein (see Figure 1.12) through a long incision much like those used today in vein harvest for coronary bypass. On the contrary, the incision was spiral (see Figure 1.13) and the lancet plunged deep to the fascia in the operation proposed by Rindfleish and Friedel in 1908. Saphenous ligation followed by

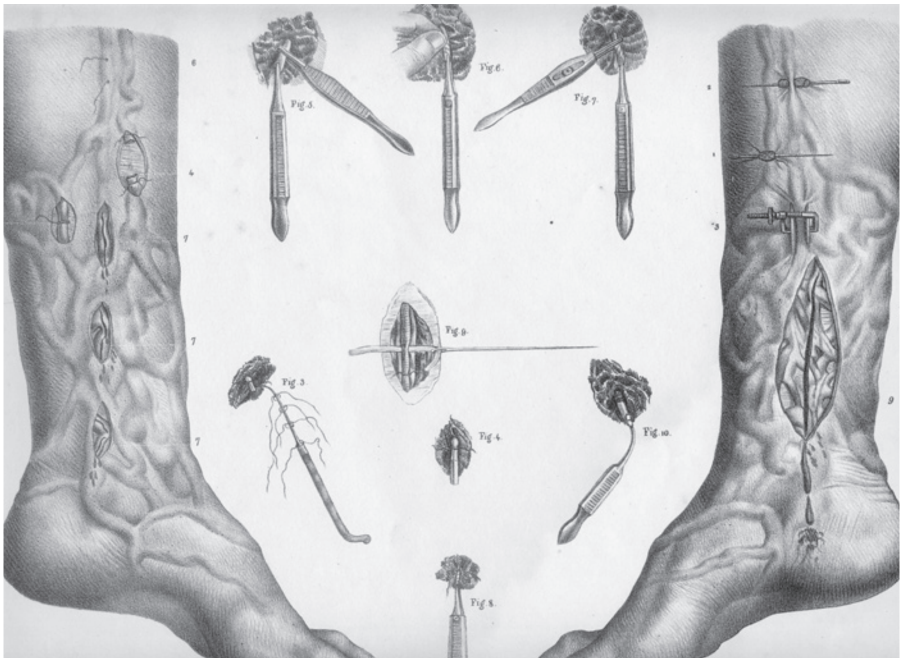


FIGURE 1.10 Techniques for venous obliteration from Davat (1), Velpeau (2), Sanson (3), Beclard (4), Wise (5), Fricke (6), and Richerand. Courtesy of Doctor Michel Georgiev.

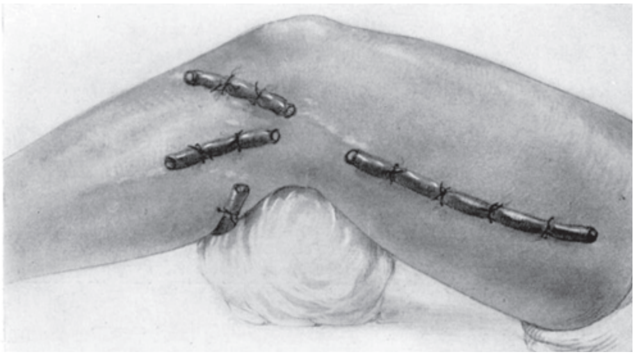


FIGURE 1.11 Velpeau's method (1826).

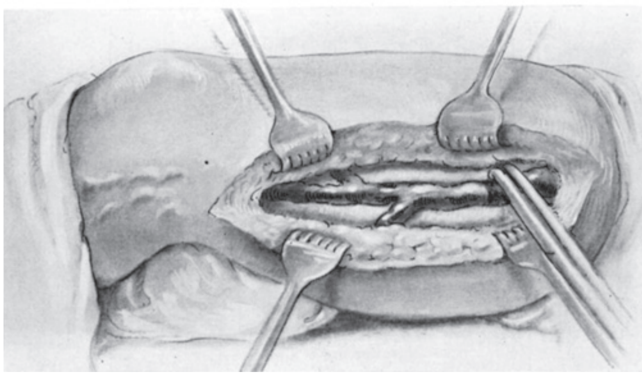


FIGURE 1.12 Great Saphenous Veins excision according to Madelung (1884).

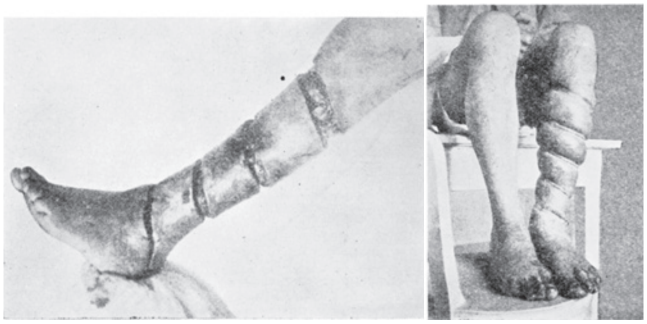


FIGURE 1.13 A) Rindfleish intervention and B) its sequelae (1908).

sclerotherapy (see Figure 1.14) was proposed by Tavel (1904), whereas Schiassi (1905) injected varicose veins at the time of surgery (see Figure 1.9).

MODERN SURGERY OF SUPERFICIAL VEINS

Modern surgery of varicose veins started in 1806, when Tommaso Rima proposed a hemodynamic treatment with ligation of the upper GSV. This operation was reproposed in 1890 by Friedrich Trendelenburg: ". . . the saphenous reflux must be the first step in control distal varicosities . . ." It consisted of a double ligation of the great saphenous just

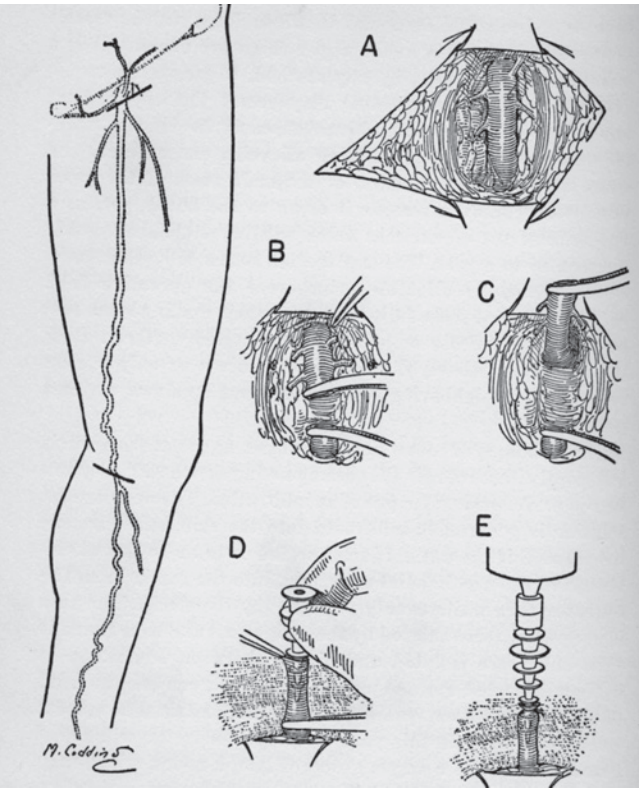


FIGURE 1.14 Sapenous interruption and its incannulation with the instrument called *pagoda*.

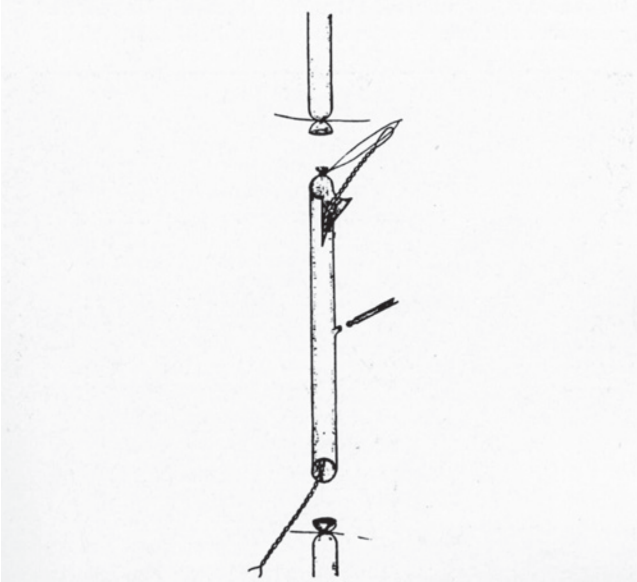


FIGURE 1.15 Keller's operation for saphenous extraction (1905).

inferior to the saphenofemoral junction, thanks to a 3 cm incision. He boasted that he could do ". . . the operation so fast that no anaesthesia was required . . ." Trendelenburg made it clear that this technique had to be applied only to those limbs in which the compression tests, described by Brodie in 1846, revealed the incompetency of the saphenofemoral valve. In 1896, Moore of Melbourne refined the Trendelenburg operation, with the skin incision performed parallel and close to the inguinal fold, almost exactly as it is today. In the same year, Thelwall Thomas emphasized the importance of ligation and division of all branches at the saphenofemoral junction.

SAPHENOUS STRIPPING

Stripping technique was introduced by Charles Mayo (1904) by using an extraluminal device. In 1905, Keller described an intraluminal stripper to extirpate the GSV (see Figure 1.15). A twisted and rigid wire was passed into the vein lumen. The wire was brought throughout its lumen at a site distal to the divided end of the vein. Its end was tied to the ligated and divided end of the varicose vein. Extracting the wire distally inverted the end of the vein into itself as the vein was extracted. This technique was then refined by van der Stricht in 1963. In 1907, Babcock modified Keller's technique and proposed to use an acorn tip and a flexible rod, which was more sophisticated than a twisted wire. His operation avoided tearing of the vein at the tributary junction, which occurs in the inversion technique. In 1920, Cole suggested to limit saphenectomy to the tract comprised between the groin and the knee. In 1930, De Takats refined the technique of Schiassi by proposing the ambulatory treatment of saphenous vein insufficiency followed by sclerotherapy. In 1947, Myers and Smith further refined the endoluminal flexible stripper.

BEYOND STRIPPING

Many effective techniques alternative to stripping were proposed in the second half of the twentieth century. First of all, the antique art of hook phlebectomy was so improved by Robert Muller (1956) to possibly operate on, with local anesthesia and small incisions, both saphenae for their entire length. Muller's stab avulsion technique was further refined and worldwide diffused in 1995 by Ricci, Georgiev, and Goldman.[9] In 1988, Claude Franceschi proposed a minimally invasive surgical approach (CHIVA) aimed to a hemodynamic correction, more than to a radical avulsion of the varicose bed, based upon a meticulous preoperative Duplex examination. External banding of the terminal saphena has been largely adopted by many centers, but its results are good only if performed in limbs with early disease, as demonstrated by Corcos et al. in 1997.[10] This procedure was refined in 2002 by Yamaki,[11] who associated

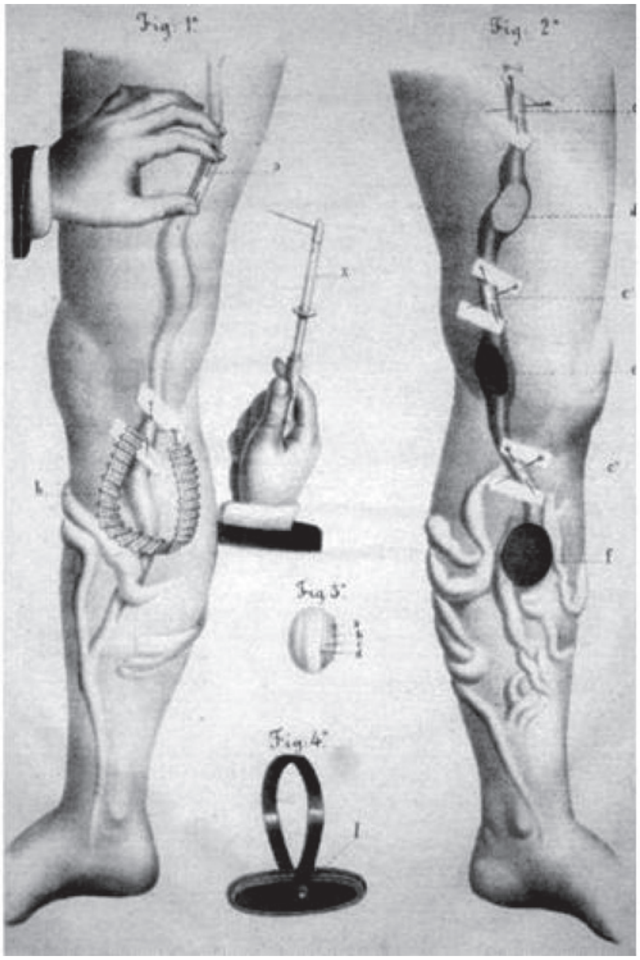


FIGURE 1.16 Gaetano Conti's method for endovascular fulguration of the Great Saphenous Vein (1854). Courtesy of Doctor Michel Georgiev.

valvuloplasty of the subterminal valve combined to the axial transposition of a competent tributary vein.

ENDOVASCULAR TECHNIQUES

Forerunner of endovascular techniques for treatment of the varicose saphena was Gaetano Conti from Naples, who, in 1854, proposed a complex method based upon "electropuncture and cauterizations of varicose veins" (see Figure 1.16). Modern endovascular techniques started in 1964 with Werner and McPheeters ("electrofulguration") and Politowski ("endovenous electrosurgical dessication"). A similar technique was proposed by Watts (1972) to treat saphenous varicosities by endovenous diathermy. In 1981, a freezing technique was proposed by Milleret and Le-Pivert to treat saphenous trunk insufficiency. This technique was refined in 1997 by Constantin, who associated ligation and division of the saphenous junction with saphenous trunk removal by a cryoprobe. The field of *physical schlerotherapy* was drastically revolutionized by two innovative techniques, which obtained the obliteration of the varicose trunks by endovascular radiofrequency and laser. Endovascular radiofrequency diffused in the late 1990s, and the first positive results were reported by Mitchell Goldman in 2000. The use of endovenous laser in the treatment of the varicose saphena was proposed first by Puglisi at the IUP World Congress of 1989 held in Strasbourg. Endovenous laser technique was deeply refined and worldwide diffused in 1999 by Boné. Many centers are still at work to evaluate exact indications and results of these techniques.

PERFORATING VEIN SURGERY

The first to suggest selective interruption of perforators to treat varicose veins was probably Remy in 1901. In 1938, Linton proposed a medial subfascial approach to treat incompetent perforators. In 1953, Cockett and Jones proposed the epifascial ligature of medial ankle perforators. Two years later, Felder recommended that the fascial incision for perforating vein ligature should be placed in the posterior midline of the calf in order to avoid placing the lower end of the incision over the ulcer itself or in the compromised skin of the medial leg: the so-called "posterior stocking seam approach." Glauco Bassi and Robert Muller used a hook for transcutaneous stripping of perforators through small incisions. Special instruments have been proposed to facilitate subfascial perforator interruption, like those of Albanese (1965) and Edwards (1976). The use of endoscopy to interrupt perforator in the subfascial space goes back to 1985 by Hauer, but only extensive technical improvements allowed its even wider and safer use.[12] Despite new techniques and instrumentations, the problem still remains open: Which perforators must be treated? And when?[13,14]

SURGERY OF THE DEEP VEINS

Ochsner and De Bakey publicized in 1943 the interruption of the inferior vena cava to prevent embolic migration from the leg. John Hunter is credited as the first to ligate it in 1739. Bottini (1893) and Trendelenburg (1910) also are credited with performing this intervention. A temporary caval ligation was proposed by Dale in 1958. In the same year, De Weese and Hunter partially interrupted the inferior vena cava by an intraluminal "hard grip." Spencer obtained caval interruption by suture plication (1965), Ravitch by stappler plication (1966), and finally, Pate by a detachable clip (1969). Mobin-Huddin described in 1967 an umbrella filter for the prevention of pulmonary embolism. This instrument was then refined by Greenfield, who introduced a steel

TABLE 1.4 Venous Reconstructive Surgery

The pioneers of venous reconstructive surgery		
1816	Travers	Sutured a traumatic lesion of the femoral vein
1830	Guthrie	Sutured a traumatic lesion of the jugular vein
1872	Eck	Porto-caval anastomosis
1878	Agnew	Lateral suture of traumatized veins
1889	Kummel	First termino-terminal anastomosis of the femoral vein
1901	Clermont	First termino-terminal anastomosis of the inferior vena cava
1912	Carrel & Guthrie	Nobel prize for improvements of vascular surgery techniques
Main steps in venous reconstructive surgery		
1950	Wanke	Surgical decompression of the left common iliac vein
1953	Kunlin	Veno-venous grafting
1954	Warren & Thayer	Great Saphenous Vein bypass of obstructed femoral veins
1958	Palma & Esperon	Cross-pubic bypass for iliac vein occlusion
1964	Stansel	Synthetic graft for caval reconstruction
1970	Husni	Sapheno-popliteal bypass for femoral venous obstruction
1982	Fiore	Reconstruction with prosthetic grafts of superior vena cava
1984	Gloviczki; Dale	Reconstruction with prosthetic grafts of inferior vena cava
1988	Zolliker	Endovascular disobliteration and stenting

filter. One year later, Eichelter and Schenk proposed a temporary caval filtration with a removable balloon.

In order to control symptoms of venous insufficiency, Parona suggested in 1894 to ligate the popliteal vein, whereas Linton suggested in 1948 to interrupt the femoral vein.

Fundamentals of reconstructive venous surgery were experienced during the nineteenth century, and in 1912, Carrel and Guthrie received the Nobel Prize for the improvements they gave to vascular surgery techniques. However, safe and effective venous interventions for venous obstructions of the trunk and limbs developed only after World War II (see Table 1.4).

THROMBECTOMY

Paré is probably the first to perform a superficial vein thrombectomy in 1545: he suggested performing an incision along the vein and squeezing it to expel the thrombus. The first thrombectomy of deep veins was performed by Lawen in 1937. In 1939, Leriche and Geisendorf associated a periarterial sympathectomy of the nonpulsatile but unoccluded femoral artery to a successful thrombectomy of the femoral vein in a patient with phlegmasia coerulea dolens. In 1966, Fogarthy described how to remove vascular obstruction by a catheter and affirmed this is the "most rationale, most effective and safest way of dealing with iliofemoral thrombosis."

SURGERY OF VALVES

The first attempt to restore valvular function was performed in 1953 by Eisemann and Malette, who proposed to produce valve-like structures by gathering folds at two sites of the venous wall opposite each other. In 1963, Psathakis proposed to entwine the tendon of the gracilis muscle between the popliteal artery and vein in order to obtain the compression of the vein during contraction of the muscle. A few years later, Ferris and Kistner proposed a transvalvular approach for internal repair of venous valve (1968). In 1984, Raju modified this technique by using a supravalvular approach. Finally, Sottiurai (1988) proposed an internal approach, modifying the original technique of Raju for supravalvular repair of the incompetent venous valves. In 1972, Hallberg proposed the external banding of the incompetent valves of deep veins by sheathing the region with a plastic tube. An extravenous valve substitute in the popliteal space was described by Psathakis in 1984. In 1982, Taheri proposed to transfer a valvulated segment of the axillary vein into the lower femoral vein to treat chronic venous insufficiency. In 1986, Jessup and Lane developed an external technique of banding incompetent valves with a silastic cuff. One year later, Kistner developed an external suture technique to "band" incompetent valves.

Reparative or substitutive surgery of venous valves improved greatly in the last years. In 1999, Dalsing introduced the use of cryopreserved venous valve allografts for the treatment of chronic deep venous insufficiency.[15] One year later, Raju, Berry, and Neglen[16] described a variation of closed external venous valve repair (transcommissural valvuloplasty). In 2001, Tripathy and Ktenidis reported a new technique of exposure of the valve commissure, called the "trapdoor" internal valvuloplasty.[17] In 2003, Pavcnik experimented with small-intestinal submucosa square-stent bicuspid venous valve in sheep jugular veins and in three patients. In the same year, Corcos[18] proposed a monocuspid valve reconstruction obtained with an intimal flap.

VENOUS ULCERS—WHY TO TREAT THEM

Ulcers of venous origins were discriminated by Spender (1866) in "varicose ulcers" and "venous ulcers" (". . . ulcers of the varicose type without varicose veins . . ."), attributing the latter to failure of deep veins. One year later, John Gay

first associated induration and bronzing of the skin as circulatory complications of venous disorders, and, having noted that varicose veins can be present for many years without any ulcer or bronzing of the skin, affirmed that ". . . ulceration is not a direct consequence of varicosity, but all of other conditions of the venous system with which varicosity is not infrequently a complication . . ." Gay's intuitions were already been explained by Fabricius (1603), who affirmed that varicose veins carry "fecaloid humours" that cause skin damage. The "bad humours" could be the hemosiderin that spreads from the capillary bed into the interstitium,[19] or other substances that produce a pericapillary fibrin cuff, poorly permeable to gases[20] or induce leukocyte trapping, migration, and release of cytotoxic substances.[21]

And Why Not to Heal Them

Only few authors devoted to the Pythagorean theory of the four humours suggested not to heal ulcers because they are considered as beneficial in expelling dangerous substances. Galen of Pergamum (130–200 AD) believed that black bile would be trapped by a healing ulcer. Thus, black bile could leak outside while the ulcer remains unhealed. If the ulcer heals, madness and other disasters would follow. Avicenna even warned to reopen varicose ulcers if these spontaneously closed. In modern times, among those reluctant to treat ulcers were Lorenz Heister (1718) and Henry Françoise Le Dran (1731). Both of them considered the ulcer to be a drain for humors that caused severe illness if not expelled. Laufman stated: ". . . A number of British surgeons took up the same cry in the eighteenth century and even into the nineteenth century(!!) . . ."

ULCER THERAPY

Modern ulcer therapy is based on 1) topical medications; 2) compressive bandage; and 3) surgery of related veins. The same was true more than two thousand years ago.

In fact, since many centuries BC ago, venous ulcers are treated by topical applications of substances (like the fig pultice used by the Prophet Isaiah), associated to bandages (Celsus) and local hygienic treatments (Hippocrates). Principles of local treatments were meticulously described in 1446 by an anonymous surgical textbook (quoted by Partsch, 2002), which treated extensively (9000 words) the treatment of leg ulcers. Four steps are reported: 1) enlargement of the ulcer mouth, to obtain drainage; 2) *mortification* (debridement); 3) *mundification* (cleansing); 4) *fleshing* (production of granulation tissue).

Ulcer therapies based only upon topical remedies were strongly criticized in 1797 by Everard Home: ". . . It must appear obvious, that there is no probability that any one medicine can ever be discovered which, whether internally administered or locally applied, shall have powers adapted to the cure of all ulcer on the legs; and it would appear, the idea that such a medicine may exist, has retarded very considerably, the advancement of our knowledge in the treatment of ulcers . . ." In addition, Brodie (1846) warned against the frequent occurrence of cutaneous sensitization due to drugs and other remedies used topically to treat ulcers.

TABLE 1.5 Walking or Bed Rest to Heal Ulcers?

1778	Benjamin Bell	Absolute bed rest
1783	Michel Underwood	Immediate mobilization
1793	John Hunter	Bed rest
1797	Thomas Baynton	Walking
1799	Whately	"*. . . to walk with no scruples . . .*"
1861	Hilton	Bed rest
1886	Dechambre	Walking

The importance of associating bandages to local treatment of ulcers was well known since Hippocrates and in 1676, the Englishman Richard Wiseman warned that venous ulcers healed by compression usually recur once the compression is discontinued. In 1771 Else tried to determine what compression therapy would do in old ulcers of the leg, without administering any internal medicine, and found it so exceedingly efficacious that he believed it will seldom fail where there is no carious bone. It has been discussed at length, whether bandaged patients must walk or if it is better that they rest on the bed (see Table 1.5). Besides clinical argumentations, ambulatory treatment of venous ulcers was justified by the analysis of the costs of hospitalization reported by Underwood in 1783 and by Philip Boyers in 1831.

Besides topical treatments, surgery of the varicose veins, when present, has been recommended since old times. Hyeronimus Fabricius of Acquapendente (1603) suggested to associate compression to double ligation and division of the varix above the ulcer. In turn, John Gay (1867) randomly divided all the veins around the ulcers by several incisions. It was only one century later, that selective interruption of perforating veins below the ulcer was emphasized by Franck Cockett. Currently, sclerotherapy is used to obliterate periulcerative varicose veins. Nevertheless, the first to perform an endovenous treatment of ulcers was Sigismond Johann Elsholz in 1665, using a chicken bone as a needle and a bladder of pigeon as a syringe.

At any case, it was suggested to invoke a "divine factor" to heal ulcers (Fabricius, 1603). On the contrary, the Roman physician Asclepiade believed that ulcer healing needs ". . . delicate massages from sweet maiden or boy, according with own preferences . . ."

TABLE 1.6 Presidents of the IUP

Erich Krieg	1959–1970
Henrik Van Der Molen	1971–1983
Jean Van Der Stricht	1983–1989
André Davy	1989–1995
Georges Jantet	1995–1999
Hugo Partsch	1999–2003
Claudio Allegra	2003–2007
Eberhard Rabe (elect)	2007–2012

ADDENDA: THE INTERNATIONAL UNION OF PHLEBOLOGY (IUP)

It was on March 24, 1959, at the Château de Meyrargues in France near Aix-en-Provence, at the close of a joint meeting of the responsible representatives of the four existing Societies of Phlebology (the French Society of Phlebology created in 1947, the Benelux Society of Phlebology created in 1957, the German Society of Phlebology created in 1958, and the Italian Society of Phlebology, which came into being at the same time) that the foundations of an International Union of Phlebology were laid. Those responsible were, Tournay and Wallois (France), van der Molen (Benelux), Krieg (Germany), and Bassi and Comel (Italy). Actually, the IUP includes the phlebological societies of more than 40 countries (see Table 1.6).

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[1]Chronology of main innovations in the field of venous medicine and surgery occurred during the last decades derived mainly by a PubMed investigation.

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C H A P T E R

2

Venous Embryology and Anatomy

GEZA MOZES and PETER GLOVICZKI

INTRODUCTION

Substantial knowledge has accumulated in recent years on development and anatomy of the venous system. Progress in medical genetics resulted in identification of genes linked to development of circulation and in recognition of growth factors affecting normal and abnormal development of blood vessels. Perfection of ultrasound technology combined with an increasing clinical interest in venous disease resulted in identification of new compartments and clinically important anatomic structures.[1] Finally, a new, clinically relevant anatomic terminology of the veins of the leg and pelvis was introduced.[2] In this chapter we discuss the embryology of the venous system and present the most frequent venous anomalies. We describe the histology of large veins and present a detailed anatomy of the veins of the trunk and the upper and lower limbs. Discussion of the anatomy of the visceral and cervical veins is beyond the scope of this review. The new terminology of veins will be used in this manuscript (see Table 2.1).

EMBRYOLOGY

During embryogenesis the earliest veins develop from capillary plexuses; these carry blood into the sinus venosus, the in-flow end of the forming heart. The right and left common cardinal veins drain directly into the sinus venosus (see Figure 2.1). The common cardinal veins form at the junction of the anterior and posterior cardinal veins on both sides. Between this junction and the heart the common cardinal veins receive the vitelline and umbilical veins. The vitelline veins initially drain the yolk sac and later the intestines. The right umbilical vein regresses completely, the left drains the placenta.[3,4]

The anterior cardinal veins drain the cranial part of the embryo and are connected to each other by a large central anastomosing channel. The segment of the left anterior cardinal vein located proximal to the anastomosis will regress. The oblique vein of the left atrium and the coronary sinus develop from the regressed proximal segment of the left anterior cardinal vein. The remaining distal segment becomes the left internal jugular vein and the anastomosis between the anterior cardinal veins forms the left brachiocephalic vein. The right internal jugular and brachiocephalic veins develop from the proximal segment of the right anterior cardinal vein. The external jugular veins develop secondarily. Failure of the regression of the proximal left anterior cardinal vein results in double superior vena cava (SVC), whereas erroneous regression on the right side results in left-sided SVC (see Figure 2.2a, b).

The posterior cardinal veins run caudal to the heart and distally develop an interconnecting iliac anastomosis. Contrary to their anterior counterparts, the posterior cardinal veins regress almost completely. Only a small proximal segment remains on the right side to form the azygos arch and the iliac anastomosis to transform into the common, external, and internal iliac and median sacral veins.

Most veins, caudal to the heart, develop from the sub- and supracardinal veins, which arise dorsal and ventral to the regressed posterior cardinal veins, respectively. The subcardinal veins anastomose with each other (subcardinal anastomosis) and with the supracardinal veins (subsupracardinal anastomosis). The majority of the left-sided cardinal veins regress. The right subcardinal vein develops to drain most of the upper, the right supracardinal vein most of the lower part of the abdomen.

Majority of the azygos system develops from the cranial part of the supracardinal veins. The infrarenal segment of the inferior vena cava (IVC) develops from the caudal right supracardinal vein. The renal segment of the IVC arises from the subsupracardinal anastomosis, a venous network located circumferentially around the aorta (renal collar). Eventually, the posterior segment of the collar regresses and the anterior part gives the left renal vein. Most of the suprarenal segment of the IVC develops from the right subcardinal vein, except for the short hepatic segment, which originates directly from hepatic sinusoids.[5] Variation in the complex development of IVC and left renal vein is not uncommon. If the right subcardinal vein fails to connect to the liver sinusoids, the suprarenal segment of the IVC will not develop, consequently the lower part of the body will be drained through the azygos system and the liver will drain directly into the heart. Double IVC (0.2–3%) occurs due to the persistence of the left supracardinal vein, therefore it usually involves only the infrarenal segment (see Figure 2.2).[6] Left-sided IVC (<0.5%) develops if persistence of the left supracardinal vein is associated with regression of the right supracardinal vein (see Figure 2.2).[7] Developmental variations of the left renal vein include persistent (circumaortic) renal collar (1–9%) and retroaortic left renal vein (1–2%) (see Figure 2.3).[8]

Capillaries of the primitive limb buds initially drain into the marginal sinuses. In the arm the ulnar portion of the marginal sinuses dominate over the radial ones, and eventually form the basilic, axillary, and subclavian veins. The

TABLE 2.1 Historic and New Anatomic Terms of Lower Extremity Veins

Historic term	New term
Greater or long saphenous vein	Great saphenous vein (GSV)
Smaller or short saphenous vein	Small saphenous vein (SSV)
Saphenofemoral junction	Confluence of the superficial inguinal veins
Giacomini's vein	Intersaphenous vein
Posterior arch vein or Leonardo's vein	Posterior accessory great saphenous vein of the leg
Superficial femoral vein	Femoral vein
Cockett perforators (I,II,II)	Posterior tibial perforators (lower, middle, upper)
Boyd's perforator	Paratibial perforator (proximal)
Sherman's perforators	Paratibial perforators
24 cm perforators	Paratibial perforators
Hunter's and Dodd's perforators	Perforators of the femoral canal
May's or Kuster's perforators	Ankle perforators

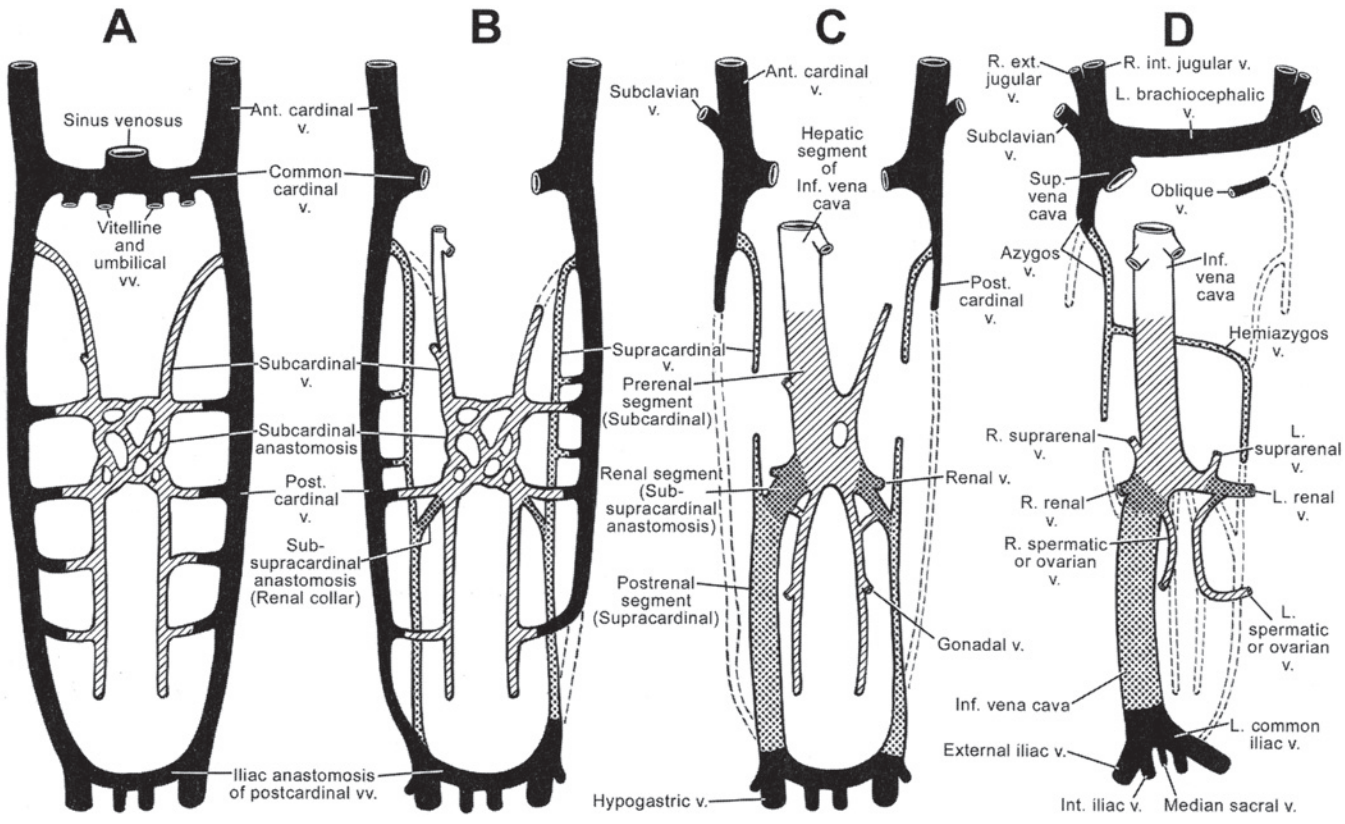

FIGURE 2.1 Embryology of the major veins (adopted from Avery LB. Developmental Anatomy, revised 7th ed. Philadelphia: WB Saunders, 1974).

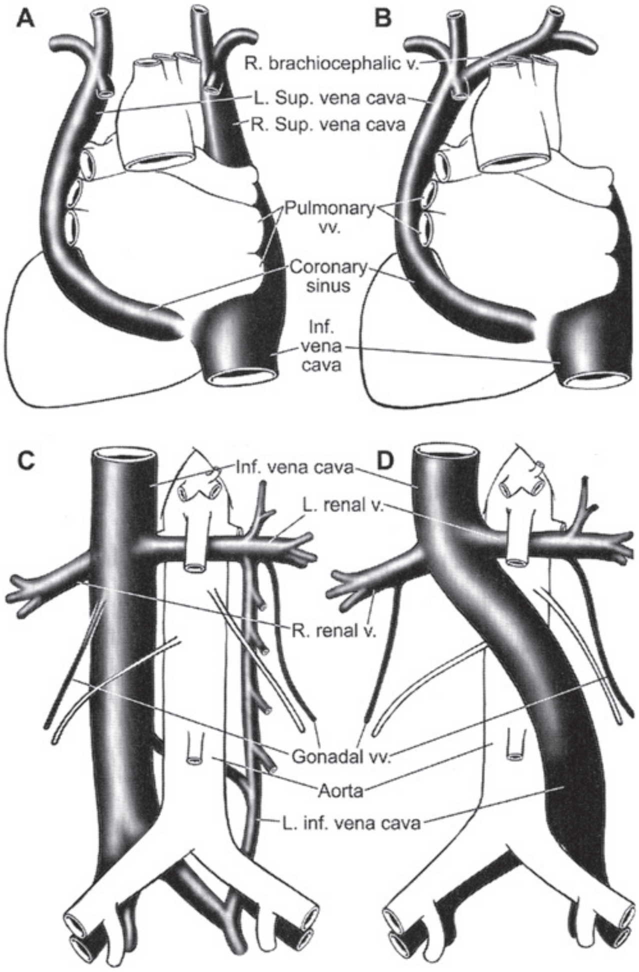

FIGURE 2.2 Developmental anomalies of the superior (SVC) and inferior vena cava (IVC). a. Double SVC (posterior view). b. Left SVC (posterior view). c. Double IVC. d. Left IVC.

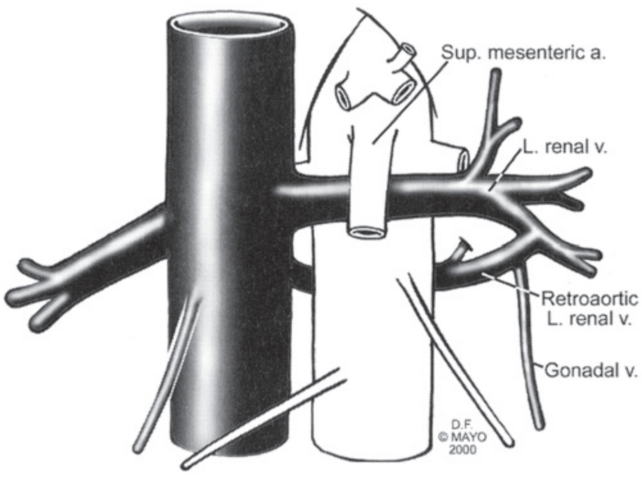

FIGURE 2.3 Circumaortic renal collar.

subclavian vein drains into the proximal anterior cardinal vein. The cephalic vein develops secondarily from segments of the radial marginal sinuses and attaches to the axillary vein later. In the leg, segments of the primitive marginal sinuses persist only distally and develop into the peroneal, anterior tibial, and small saphenous veins. The great saphenous vein originates from the posterior cardinal vein and later gives off the femoral, popliteal, and posterior tibial veins.

HISTOLOGY

The venous wall has three layers: intima, media, and adventitia. The intima is made up by endothelial cells and an underlying thin connective tissue layer. Valves are formed by infolding of the intima, therefore they are covered with endothelium on both sides and have a very thin connective tissue skeleton. Venous valves are bicuspid. The veins are distended at the base of the valves, probably secondary to the effects of local flow reversal. The border of the intima is marked by the internal elastic lamina: a layer of thick elastic fibers. The internal elastic lamina is well developed only in large veins; it is incomplete in medium-sized and absent in small ones. The media is composed of smooth muscle cells and connective tissue fibers, most of which is collagen. Larger superficial veins, such as the GSV, have thick muscular media with the ability of significant contraction. Smaller tributaries of the GSV have thinner media, and therefore are more prone to varicosity. Media of the deep calf veins contain plenty of collagen, providing better wall strength. More central deep veins, such as femoral, iliac, axillary, and subclavian veins, contain less and less smooth muscle cell. The media of the superior and inferior vena cava is built up almost exclusively from connective tissue. The adventitia is poorly differentiated from the media, in particular in larger veins. It consists of some loose connective tissue with vasa vasorum and nerve fibers.[9,10]

ANATOMY OF THE THORACIC VEINS

The superior vena cava (SVC) starts at the confluence of the brachiocephalic veins behind the first right costal cartilage, and ends at the level of the third right costal cartilage where it drains into the right atrium. The SVC is about 7 cm long and 2 cm wide. Halfway along its course, before it enters the pericardium, the SVC receives the azygos arch. The brachiocephalic veins are formed at the confluence of the subclavian and internal jugular veins behind the sternoclavicular joints (see Figure 2.4). The right brachiocephalic vein is short, about 2–3 cm, and lies anterior to the innominate artery.[7] The left one is about 6 cm long and courses obliquely behind the manubrium from left to right, anterior

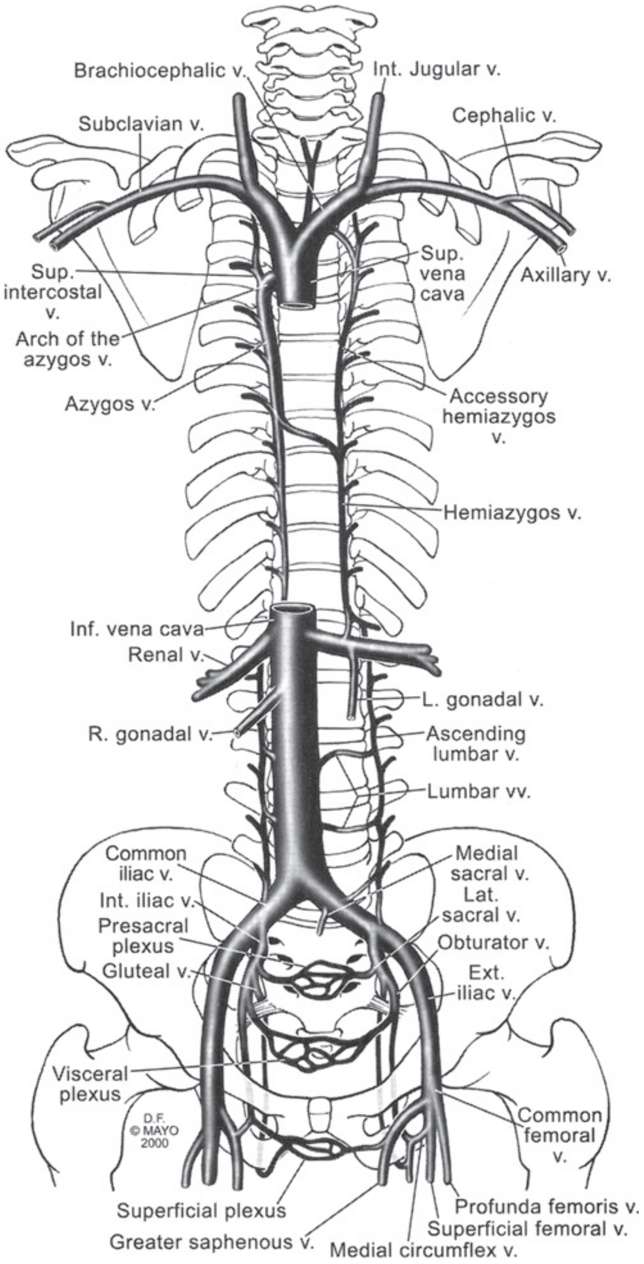

FIGURE 2.4 Thoracic and retroperitoneal veins.

to the left subclavian, common carotid arteries, and superior to the aortic arch. Major tributaries of the brachiocephalic veins are the vertebral, internal thoracic, and inferior thyroid veins. The first intercostal vein drains into the brachiocephalic veins on both sides. The left superior intercostal vein is connected to the left brachiocephalic vein, whereas on the right it joins the azygos vein. There are no valves in either the SVC or the brachiocephalic veins.

The azygos-hemiazygos system forms an H-shaped network in the posterior mediastinum, anterior to the body of the thoracic vertebrae (see Figure 2.4). The azygos vein gives the entire right arm of the H, the hemiazygos gives the left lower and the accesory hemiazygos vein the left upper segment. The azygos vein starts at T12 to L2 with the confluence of the right ascending lumbar and subcostal veins. The azygos vein ascends on the right side up to the level of T4, then passes anterior to form an arch joining the SVC. Major tributaries of the azygos vein are the right posterior fifth to eleventh intercostal veins and the right superior intercostal vein draining the second to fourth intercostal veins. The hemiazygos vein starts similar to the azygos vein but on the left side of the vertebral column at T12–L2. It courses cranial and at the level of T8 it crosses over to join the azygos vein. Major tributaries of the hemiazygos vein are the left posterior eighth to eleventh intercostal veins. The accessory hemiazygos vein has more variation than the azygos and hemiazygos veins. Usually it drains the left superior intercostal vein (which in turn drains the left second to fourth intercostal veins) and the left posterior fifth to seventh intercostal veins. At the level of T7 it either crosses over to the right and joins the azygos or stays on the left and joins the hemiazygos vein. If the connection between the accessory hemiazygos and the rest of the azygos-hemiazygos system is not developed, the accessory hemiazygos vein will drain through the left superior intercostal vein into the left brachiocephalic vein. The azygos-hemiazygos system receives several small veins from the viscera of the chest and freely anastomoses with the vertebral venous plexuses as well. The azygos-hemiazygos system provides an important collateral pathway in case of IVC or SVC obstruction.[7]

ANATOMY OF THE UPPER EXTREMITY VEINS

The dorsal and palmar digital veins join to form the metacarpal veins, which drain into the superficially located dorsal venous network of the hand. The cephalic and basilic veins arise from this network on the radial and ulnar side of the wrist, respectively. The superficial veins on the palmar side of the hand are richly anastomosed to the deep veins. A superficial and a more proximal deep venous arch is formed from the interconnection of the palmar veins and parallel the corresponding arterial arches.

The cephalic vein originates at the anatomical snuff box from the dorsal venous network. It courses over the distal radius to the ventral aspect of the forearm and ascends on the lateral side of the arm. The cephalic vein runs in the deltopectoral groove, it enters the infraclavicular fossa behind the pectoralis major muscle and pierces the clavipectoral fascia before empting into the axillary vein (see Figure 2.5). The basilic vein begins on the ulnar side of the wrist, passes along the ulnar aspect of the forearm, and courses more ventrally at the level of the elbow. Above the elbow

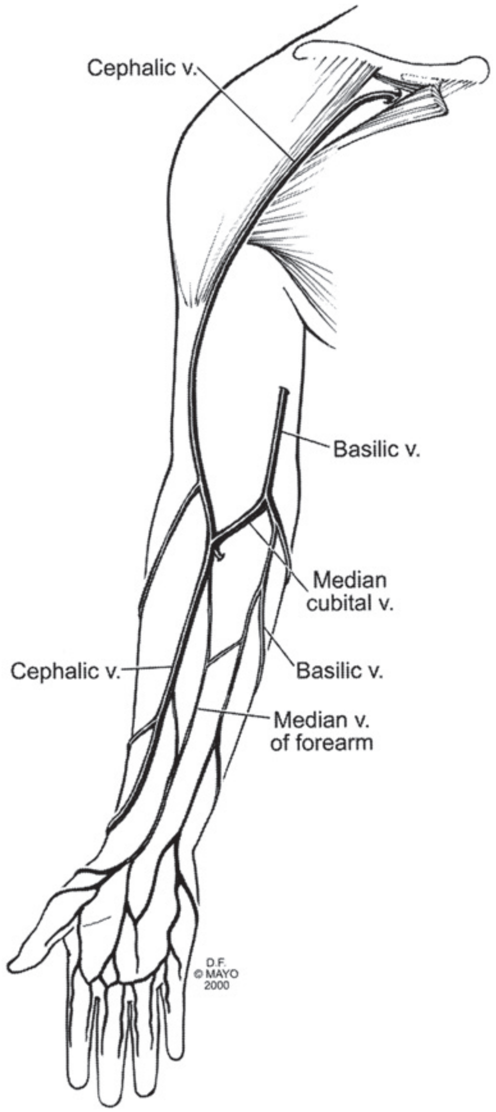

FIGURE 2.5 Upper extremity superficial veins.

the basilic vein runs medial to the biceps and at about midway in the upper arm it perforates the deep fascia and joins the brachial vein. After receiving the brachial vein, the basilic vein continues in the axillary vein. The median cubital vein connects the cephalic and basilic veins in the antecubital fossa. The medial antebrachial vein originates from the superficial palmar venous plexus and runs on the ventral side of the forearm. It joins either the cephalic or basilic vein or both in the proximal forearm. The accessory cephalic vein originates from the dorsal venous plexus on the ulnar side and crosses over dorsally to join the cephalic vein in the forearm. Variations in the anatomy of superfical arm veins are countless.

Deep veins of the hand join to form the paired radial, ulnar, and interosseus veins, which accompany the corresponding arteries. The three pairs of deep veins of the forearm form the brachial veins at the level of the elbow. The paired brachial veins join the basilic vein to form the axillary vein at the lower border of the teres major muscle (at the lateral border of the scapula on an antero-posterior chest x-ray). The axillary vein is located medial and inferior to the axillary artery and the medial cord of the brachial plexus lies between the two vessels. The axillary vein ends at the outer border of the first rib where it becomes the subclavian vein. The subclavian vein runs posterior and superior to the subclavian artery and recives its only major tributary, the external jugular vein. The subclavian vein ends at the medial border of the scalenus anterior muscle where it joins the internal jugular vein to form the brachiocephalic vein.

There are valves in the superficial and deep veins of the arm, although they are not so numerous as in the leg. Valves in the axillary vein usually are located proximal to the junction with the brachial and cephalic veins. The subclavian vein has a valve just proximal to the confluence of the external jugular vein. Upper extremity venous return is maintained mainly by the work of the heart without significant contribution of a muscle pump. Therefore the valves are less important from a functional standpoint. Perforators between the deep and superficial veins are scarce.

ANATOMY OF THE ABDOMINAL AND PELVIC VEINS

The inferior vena cava (IVC) begins at the confluence of the common iliac veins and ascends on the right side of the vertebral column, passes through the tendinous portion of the diaphragm, and after a short course (approximately 2.5 cm) in the chest it terminates in the right atrium at the level of T9. In the upper abdomen the IVC is located posterior to the duodenum, the head and neck of the pancreas, the lesser sac, and the liver. The intrahepatic portion of the IVC lies in a groove along the posterior aspect of the caudate lobe. Tributaries of the IVC are the paired lumbar and renal veins and the hepatic veins, additionally on the right side the right gonadal, suprarenal, and inferior phrenic veins also drain into the IVC (see Figure 2.4). The left gonadal and suprarenal veins join the left renal vein, the left inferior phrenic vein drains into the left suprarenal vein. In case of IVC obstruction, communication between the veins of the thoracic and abdominal wall (thoracoepigastric, internal thoracic, and epigastric veins), the lumbar-azygos anastomosis, and the vertebral plexuses provide important collateral pathways.

The common iliac veins begin at the sacroiliac joint on both sides and end at L5, where they form the IVC. The only tributary of the right common iliac vein is the right ascending lumbar vein; the left common iliac vein drains the left ascending lumbar and median sacral veins (see Figure 2.4).

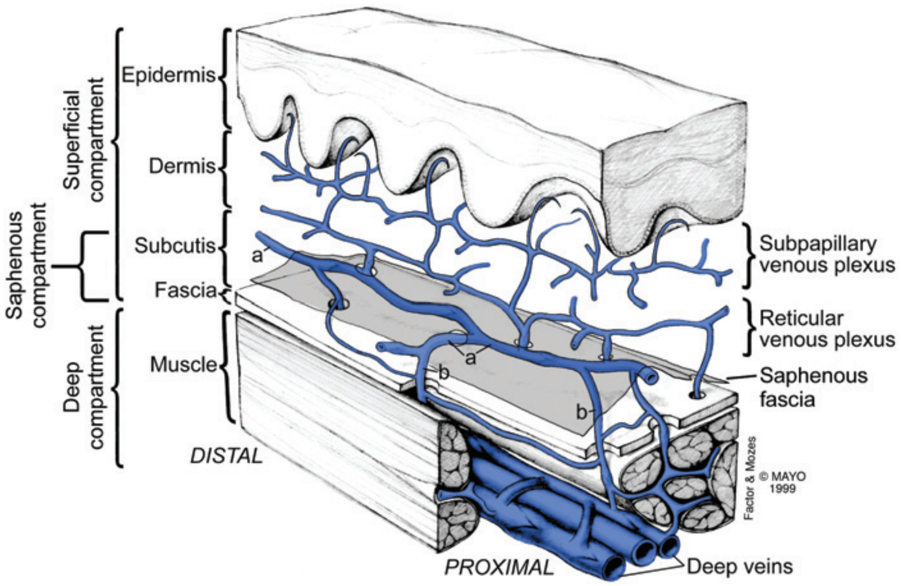

FIGURE 2.6 Relationship between the fascia and veins of the lower extremity. The fascia covers the muscle and separates the deep from the superficial compartment. Superficial veins (a) drain the subpapillary and reticular venous plexuses, and are connected to deep veins through perforating veins (b). The saphenous fascia invests the saphenous vein. The saphenous compartment is a subcompartment of the superficial compartment.

The right common iliac vein lies postero-lateral to the right common iliac artery. The distal segment of the left common iliac vein is medial and posterior to the left common iliac artery, the proximal segment is posterior to the right iliac artery and distal aorta. Compression of the proximal left common iliac vein may occur due to the overlying arterial structures. The external iliac vein starts at the level of the inguinal ligament, it courses along the pelvic brim and ends anterior to the sacroiliac joint where the external and internal iliac veins form the common iliac vein. On the right the distal external iliac vein is medial to the artery; however, as it ascends, more proximally, it courses posterior to it. The left external iliac vein remains medial to the artery along its entire course. Tributaries of the external iliac vein are the inferior epigastric, deep circumflex iliac, and pubic veins. The internal iliac vein runs postero-medial to the internal iliac artery on both sides. The short trunk of internal iliac vein is formed by the confluence of extra and intrapelvic venous tributaries. The extrapelvic tributaries include the gluteal (superior and inferior), internal pudendal, and obturator veins, which drain the pelvic wall and the perineum. Intrapelvic tributaries of the internal iliac vein are the lateral sacral and visceral (middle rectal, vesical, uterine, and vaginal) veins, which drain the presacral and pelvic visceral venous plexuses (rectal, vesical, prostatic, uterine, and vaginal).

Both the IVC and the common iliac veins are valveless. There is usually one valve in the external iliac vein, however often it is without any valves.

ANATOMY OF THE LOWER EXTREMITY VEINS

Thorough knowledge of the fascial compartments of the leg is a prerequisite of understanding the relationship between superficial and deep veins. The fascia surrounding the calf and thigh muscles separates two compartments: the superficial compartment, consisting of all tissues between the skin and the fascia, and the deep compartment, which includes all tissues between the fascia and the bones (see Figure 2.6).[11] Superficial veins run in the superfical, deep veins in the deep compartments. Perforating veins pierce through the fascia and connect the superficial to deep veins.[12] Communicating veins connect veins within the same compartment: superficial to superficial or deep to deep veins. The saphenous veins are covered by a fibrous sheath, the saphenous fascia. The saphenous fascia is thinner than the deep fascia and it is more pronounced in the upper-mid thigh, than more distally.[1,13] The space between the saphenous and muscular deep fascia is the saphenous compartment. The saphenous compartment is a subcompartment of the superficial compartment.

The superficial venous system of the foot is divided into the dorsal and plantar subcutaneous venous network (see Figure 2.7). Superficial vein tributaries drain blood into the dorsal venous arch on the dorsum of the foot at the level of the proximal head of the metatarsal bones. The medial and lateral end of this arch continues through the medial and

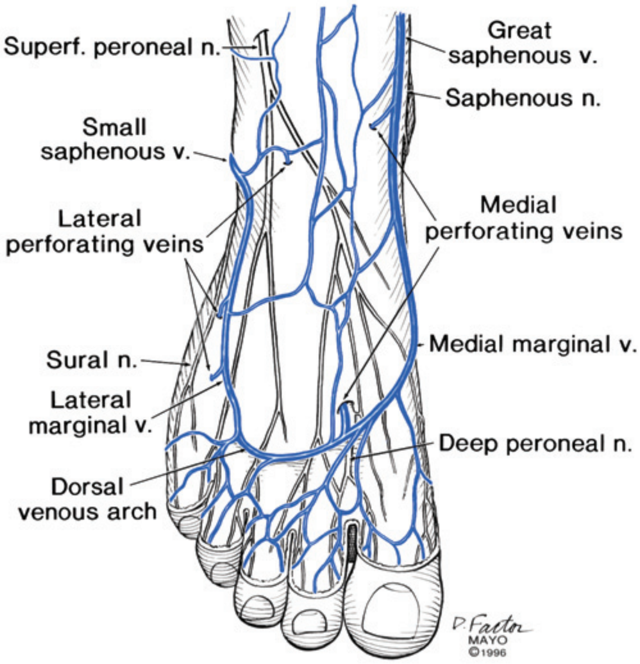

FIGURE 2.7 Superficial and perforating veins of the foot and ankle.

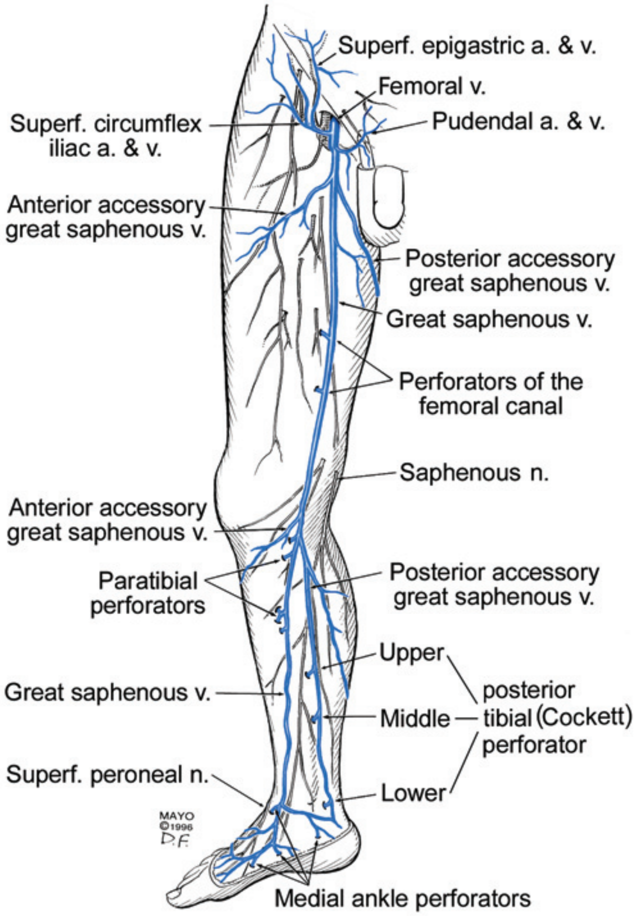

FIGURE 2.8 Superficial and perforating veins of the leg.

lateral marginal vein into the great (GSV) and small saphenous veins (SSV), respectively.

Small superficial veins drain the subpapillary and reticular plexuses of the skin and subcutaneous tissues to form bigger tributaries, which eventually all connect to the saphenous veins.[14,15] The GSV begins just anterior to the medial ankle, crosses in front of the tibia, and ascends medial to the knee (see Figure 2.8).[16–18] Proximal to the knee, the GSV ascends on the medial side of the thigh and enters the fossa ovalis 3 cm inferior and 3 cm lateral to the pubic tubercle.[19] The GSV is doubled in the calf in 25% of the population, in the thigh in 8%.[20] The saphenous nerve runs in close proximity to the GSV in the distal two-thirds of the calf. Accessory great saphenous veins are frequently present and they run parallel to the GSV both in the thigh and in the leg; they lie either anterior, posterior, or superficial to the main trunk. The posterior accessory GSV of the leg (Leonardo's vein or posterior arch vein) is a common tributary, it begins posterior to the medial malleolus, ascends on the posteromedial aspect of the calf, and joins the GSV distal to the knee (see Figure 2.8). The anterior accessory GSV of the leg drains the anterior aspect of the leg below the knee. The posterior accessory GCV of the thigh, if present, drains the medial and posterior thigh.[11] The anterior accessory GSV of the thigh collects blood from the anterior and lateral side of the thigh (see Figure 2.8). The anterior and posterior accessory GSVs join the GSV just before it ends at the confluence of superficial inguinal veins (saphenofemoral junction). The superficial circumflex iliac, superficial epigastric, and external pudendal veins join each other and the distal GSV to form the confluence of superficial inguinal veins (saphenofemoral junction) (see Figure 2.9).[21] Rarely, the GSV terminates high on the lower abdomen or joins the femoral vein very low and the superficial inguinal veins empty individually into the femoral vein.[22] Other occasional tributaries of the GSV in the groin include the posterior and anterior thigh circumflex veins.

The small saphenous vein (SSV) lies lateral to the Achilles tendon in the distal calf (see Figure 2.10).[23] In the lower two-thirds of the calf the SSV runs in the subcutaneous fat, then it pierces the fascia and runs between the two heads of the gastrocnemius muscle. In the popliteal fossa at about 5 cm proximal to the knee crease, the main trunk of the SSV drains into the popliteal vein. A smaller vein, the cranial extension of the SSV, frequently continues in cephalad direction (see Figure 2.10).[24] Uncommonly the main trunk of the SSV continues without draining into the popliteal vein and eventually empties into the femoral vein or GSV.[11] The intersaphenous vein (vein of Giacomini) is a communicating vein connecting the SSV to the GSV in the

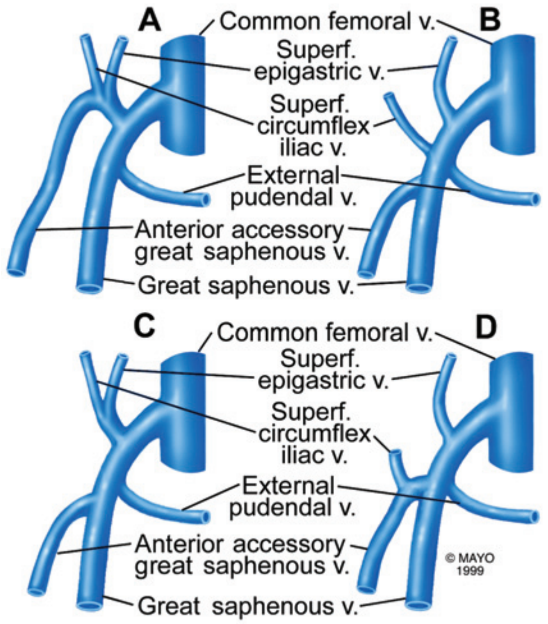

FIGURE 2.9 Common variations (a. –33%, b. –15%, c. –15%, d. –13%) in the anatomy of the confluence of inguinal veins (saphenofemoral junction).

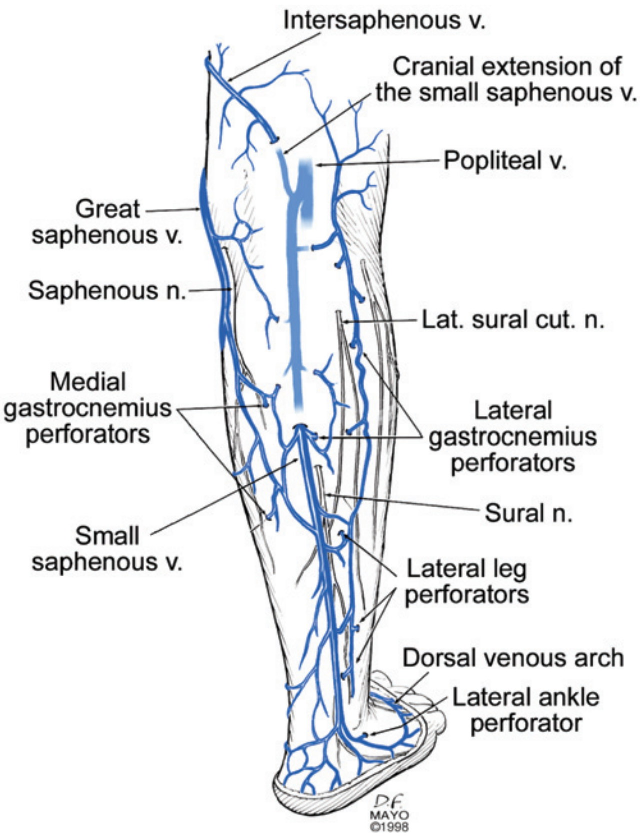

FIGURE 2.10 The small saphenous vein and lateral venous system of the calf.

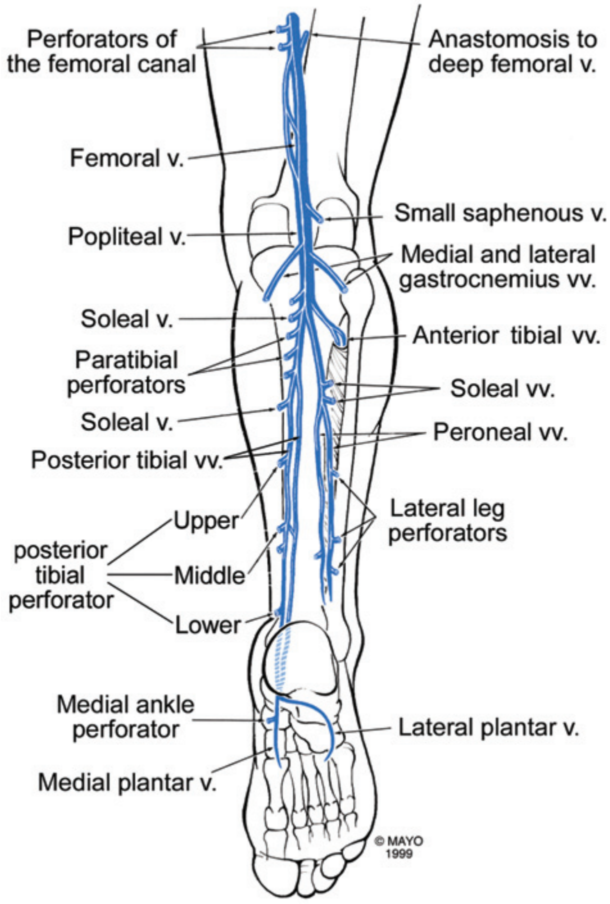

FIGURE 2.11 Deep veins of the foot and calf.

posterior-medial thigh. The sural nerve courses along the SSV in the distal calf. Superficial veins of the lateral leg and thigh form the lateral venous system. The lateral venous system is drained through multiple small tributaries into the GSV and SSV.

Deep veins of the foot form two divisions: the plantar and the dorsal veins. The richly anastomosing deep plantar venous arch drains the plantar digital veins through the plantar metatarsal veins. The deep plantar venous arch drains into the medial and lateral plantar veins, which in turn continue in the posterior tibial veins behind the medial ankle (see Figure 2.11).[25] On the dorsum of the foot the pedal vein drains the deep dorsal digital veins through the dorsal metatarsal veins. The pedal vein continues in the anterior tibial veins. Pairs of the posterior and anterior tibial and peroneal veins accompany the corresponding arteries, and all drain into the popliteal vein (see Figures 2.11 and 2.12). Large soleal and gastrocnemius (medial, lateral, and intergemellar) veins drain venous sinuses of calf muscles and join the popliteal vein. Venous sinuses are closely related to deep veins. They are embedded in the belly of calf muscles, such

as the soleus and gastrocnemius, and are able to dilate and hold a large amount of blood. With the contraction of calf muscles at walking the blood is pumped to more proximal deep veins (calf muscle pump). The popliteal vein continues into the femoral vein as it is passing through the adductor canal. The popliteal and femoral veins are frequently duplicated.[26] Distally the femoral vein runs lateral to the femoral artery; however, more proximally it runs medial to it. The deep femoral (*profunda femoris*) vein joins the femoral vein to form the common femoral vein at about 9 cm below the inguinal ligament.[27] The common femoral vein is medial to the common femoral artery and it becomes the external iliac vein at the level of the inguinal ligament. The GSV joins the common femoral vein at the confluence of the superficial inguinal veins. Other tributaries of the common femoral vein are the circumflex femoral veins (lateral and medial). In the distal thigh the femoro-popliteal segment frequently communicates through a large collateral with the deep femoral vein providing an important alternative avenue for venous drainage in case of femoral vein occlusion. The sciatic vein, the main trunk of the primordial deep venous system, runs along the sciatic nerve.

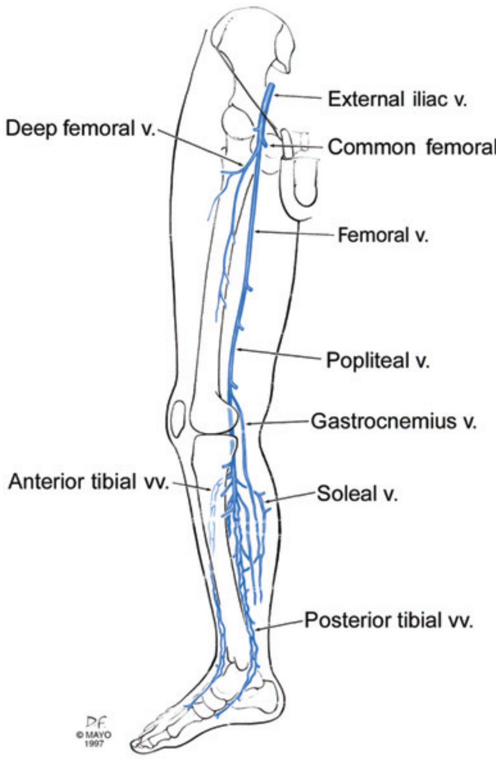

FIGURE 2.12 Deep veins of the leg.

There are as much as 150 perforating veins (PVs) in the lower extremity; however, only a few of these are clinically important. Significant variation exists in the location of individual PVs; however, distribution of clusters of PVs follows a predictable pattern. Dorsal, plantar, medial, and lateral foot perforators are the main groups of PVs in the foot.[28] A large PV runs between the first and second metatarsal bones and connects the superficial dorsal venous arch to the pedal vein.[29] Clusters of PVs at the ankle are the anterior, medial, and lateral ankle perforators (see Figure 2.13).[30] The medial calf perforators have two groups: posterior tibial and paratibial PVs. Three groups (lower, middle, upper) of posterior tibial PVs (Cockett I–III perforators) connect the posterior accessory GSV to the posterior tibial veins (see Figures 2.8, 2.11, and 2.13).[31,32] The paratibial perforators drain the GSV

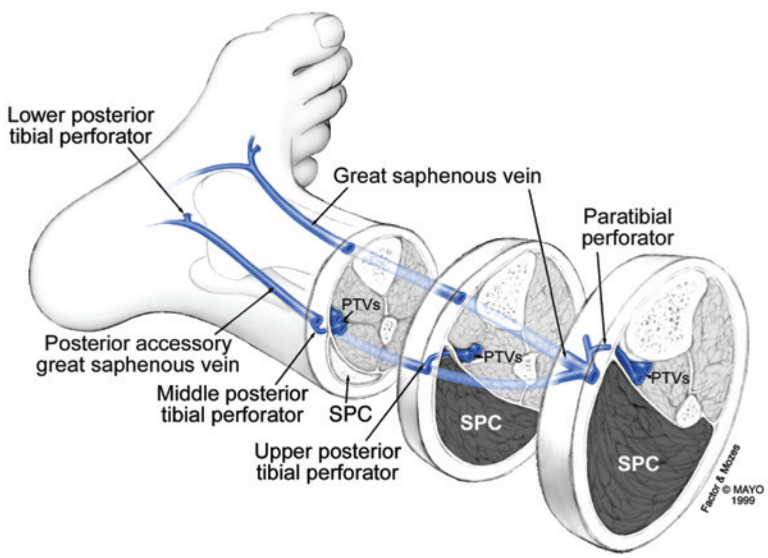

FIGURE 2.13 Relationship of the posterior tibial perforators to the deep and superficial posterior compartments (SPC) of the calf (PTVs, posterior tibial veins).

into the posterior tibial veins.[33,34] Other perforators of the leg below the knee are the anterior, lateral, medial, and lateral gastrocnemius; intergemellar and Achillean PVs (see Figure 2.11). Infra- and suprapatellar and popliteal fossa PVs are located around the knee. Perforators of the femoral canal connect tributaries of the GSV to the femoral vein (see Figure 2.8). Inguinal perforators drain into the femoral vein in the proximal thigh.

Valves in superficial veins of the lower extremity usually are located near to the termination of major tributaries. Some valves are well developed with marked sinusoid dilation at their base, others are more delicate in their structure. In the GSV there are about six valves, with more valves located below than above the knee. A nearly constant valve of GSV is at 2–3 cm distal to its confluence with the femoral vein. Valves in the SSV are closer to each other than in the GSV. Valves in communicating branches between the SSV and GSV are oriented to direct blood from the small to the great saphenous vein. Similar to superficial veins, deep veins have more valves in the calf than in the thigh. Tibial veins are densely packed with valves, whereas there are only one or two valves in the popliteal vein. In the femoral vein there are three to five valves, with one of them located just distal to the junction of the deep femoral vein. There is usually one valve in the common femoral vein. Major PVs have one to three valves, all located below the level of the fascia, that direct flow toward the deep veins. Small PVs are usually valveless. PVs of the foot are without any valves or with valves that direct flow toward the superficial veins.

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CHAPTER

3

Epidemiology of Chronic Peripheral Venous Disease

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INTRODUCTION

The term *chronic venous disease*, or more specifically of interest here, *chronic peripheral venous disease* (CPVD) has been used more generally to refer to either visible and/or functional abnormalities in the peripheral venous system. The most widely used classification of such abnormalities is the CEAP (Clinical, Etiological, Anatomic, Pathophysiologic), which includes both anatomic (superficial, deep, or perforating veins) and pathophysiologic (reflux, obstruction, both) categories.[1]

The CEAP classification was created by an international committee of clinical experts, and reflects the clinical situation in patients typically referred to a vascular specialist for clinically significant venous disease. In contrast to the clinical situation, population studies of CPVD typically have focused on broader categories determined by visual inspection only. The three major categories of interest have been varicose veins (VV), chronic venous insufficiency (CVI), and venous ulcers. However, there has not been a standard definition of these categories. VV has been defined both including and excluding telangiectasias (spider veins), and at differing levels of visible disease severity. CVI typically has been defined by skin changes and/or edema in the distal leg. Venous ulcers, both active and healed, have been defined by visual inspection and subjective inference as to etiologic origin.

Two studies have now reported results on defined free-living populations with simultaneous assessment of both visible abnormalities and functional impairment by Duplex ultrasound.[2,3] The Duplex examination for the San Diego Population Study (SDPS) determined both obstruction and reflux, whereas the Edinburgh study determined only the latter. These studies have rasied some questions regarding the validity of the assumptions based on earlier population studies and regarding the utility of the CEAP classification, at least as applied to largely healthy population samples. Specifically, the general concept that visible disease necessarily implied underlying functional disease, and vice versa, was true in the large majority of affected limbs, but not universally so.

Although these discrepancies occurred in a minority of cases, they were frequent enough to lead us to separately classify visible and functional CPVD in each limb evaluated in the SDPS. Specifically, we classified each limb into four visible categories: normal, telangectasias/spider veins (TSV), VV, and trophic changes (TCS), the latter category being one or more of hyperpigmentation, lipodermatosclerosis, or active or healed ulcer. The presence/absence of edema was not by itself a criterion for TCS. For functional disease, we determined the presence of obstruction and reflux separately for the superficial, perforating, and deep systems. The presence of either reflux or obstruction in superficial or deep veins was categorized as functional disease, and because of small numbers, abnormalities of the perforating veins were considered as deep disease. Three functional categories were defined: normal, superficial functional disease (SFD), and deep functional disease (DFD). Here, the term “functional” is essentially interchangeable with “anatomic.” Also, in this population study obstruction was uncommon, and virtually all legs with obstruction also had reflux, such that SFD and DFD essentially refer to reflux.

In addition to separately assessing edema, we asked about a history of superficial venous thrombosis (SVT) and deep venous thrombosis (DVT), with or without pulmonary embolism.

Table 3.1 shows the prevalence of various manifestations of CPVD in the SDPS by age, gender, and ethnicity. Spe-

cifically, prevalence rates are given for TSV, VV, TCS, SFD, DFD, edema on physical examination, and SVT and DVT by history.

AGE AND CVPD

Using mutually exclusive categories for both visible and functional CVPD, we found a graded relationship with increasing age for VV, with those aged 70–79 years having nearly twice the prevalence of those aged 40–49 years. TSV also increased with age, but this difference was obscured by the mutually exclusive categories with increasing numbers of participants with TSV also having VV or TCS at older ages. TCS showed the most dramatic age-related increase, with the oldest age group having more than four times the prevalence of the youngest.[3] These findings for visible disease are consistent with most previous population studies, which generally have found a linear increase in TSV or VV with age (reviewed in Reference 4). Earlier studies typically defined CVI only by venous (assumed) ulcers, and reported exponential increases in CVI with age, findings similar to the dramatic age increase we reported for the broader TCS category.

For functional CVPD, SFD was more than twice as common and DFD was 64% more common in the oldest age group. SFD showed both a higher prevalence and a steeper age gradient than did DFD.[3] The only other population data on functional disease were from the Edinburgh study and were limited to reflux, and showed similar gradients with age.[2]

Edema was strongly age-related as expected, but history of SVT and DVT were somewhat less so, perhaps reflecting selective recall bias in older participants.[3] Nonetheless, our data for DVT overall are quite similar to the lifetime prevalence in a large population-based study.[5]

GENDER AND CPVD

For visible disease, we found nearly twice as much VV in women as in men, but TCS were 50% more common in men.[3] These findings for VV are consistent with earlier studies, but earlier studies also have suggested a small excess of CVI in women, in contrast to our findings for the broader category of TCS. However, more concordant with our findings, the Edinburgh study reported that CVI was twice as common in men as women. For functional CPVD, only the Edinburgh study has comparable data, and only for reflux, and found a gender ratio for functional disease similar to the SDPS.

Edema was about 50% more common in men than women, consistent with a 50% greater history of DVT in men.[3] The Edinburgh group reported more edema in women, but a discordance with CVI being more common in men.[2] In contrast, in our study a history of SVT was more than twice as common in women, which has been linked to hormonal factors and pregnancy.[6,7]

ETHNICITY AND CPVD

The SDPS reported data for four ethnicities, non-Hispanic White, Hispanic, African-American, and Asian. Non-Hispanic Whites showed the highest prevalence of CPVD, with only 14.3% with a normal examination. Non-Hispanic Whites had the highest rates of TSV, TCS, and DFD, and the second highest rates (after Hispanics) of VV and SFD. African-Americans and Asians had a somewhat lower prevalence of CPVD. Consistent with the visible and functional findings, Non-Hispanic Whites also had the highest rates of edema and DVT by history, and Hispanics the highest rate of SVT by history.[3]

Several previous studies have suggested a higher prevalence in developed than developing countries, although these studies are not entirely consistent (reviewed in Reference 4). The SDPS is the first population study to evaluate multiple ethnic groups who were residents of the same geographical area.

CONCORDANCE OF VISIBLE AND FUNCTIONAL DISEASE

Figure 3.1 shows the concordance of visible and functional disease in the individual 4422 legs of the 2211 participants for this analysis. The majority of legs showed TSV, but the majority of legs were also functionally normal. If we consider TSV as a “normal” visible finding, visible disease would be defined as VV or TCS, and functional disease as SFD or DFD. The concordance between visible and functional disease was 92%, 17.4% concordant for disease presence and 74.6% concordant for disease absence. Discordance was thus 8%, 4.9% of the legs with visible but not functional disease, and 3.1% with functional but not visible disease. Surprisingly, 21% of all legs with VV were normal functionally (3.7%/17.7%), as were 26% of all legs with TCS (1.2%/4.6%). Thus, although the concordance was strong, visible disease did not invariably mark underlying functional disease, and functional disease was sometimes present in the absence of any visible venous disease.[3]

CONCORDANCE OF CPVD WITH EDEMA, SVT, AND DVT

Table 3.2 shows edema on examination and SVT and DVT by history, cross-classified by visible and functional disease. Significant differences from the normal/normal

TABLE 3.1 Visible and Functional Chronic Venous Disease, Edema, and Thrombotic Events by Strata of Sex, Age, and Ethnicity, San Diego, California, 1994–1998

				Visible disease, %				Functional disease, %			Edema and thrombotic events, %		
Study group		N	%	NL	TSV	VV	TCS	NL	SFD	DFD	Edema	STE	DTE
All subjects		2211	100	19.0	51.6	23.3	6.2	72.1	19.0	9.0	5.8	2.4	3.2
Men		780	35.3	33.6	43.6	15.0	7.8	75.6	13.1	11.3	7.4	1.5	4.0
Women		1431	64.7	11.0	55.9	27.7	5.3	70.1	22.2	7.8	4.9	2.8	2.7
Age, yrs	<50	534	24.2	33.0	47.9	16.9	2.3	81.8	11.2	6.9	2.6	2.1	2.4
	50–59	608	27.5	22.5	52.8	20.7	4.0	78.0	14.5	7.6	4.1	2.5	2.5
	60–69	557	25.2	12.4	52.8	26.0	8.8	66.1	23.5	10.4	6.1	2.2	3.8
	70+	512	23.2	7.4	52.5	29.9	10.2	61.3	27.3	11.3	10.7	2.7	4.1
Ethnicity	NHW	1282	58.0	14.3	54.8	24.0	6.9	69.7	20.0	10.3	7.8	2.6	4.4
	Hispanic	338	15.3	18.9	50.0	26.3	4.7	71.0	22.8	6.2	1.8	3.6	1.5
	Afr. Am.	318	14.4	27.7	45.3	20.8	6.3	76.7	16.4	6.9	4.1	0.9	1.9
	Asian	273	12.4	31.1	45.4	18.7	4.8	78.8	12.5	8.8	3.3	1.5	1.1

Abbreviations: NL = normal, TSV = telangiectasias and spider veins, VV = varicose veins, TCS = trophic changes, SFD = superficial functional disease, DFD = deep functional disease, NHW = Non-Hispanic White, Afr. Am. = African-American, STE = superficial thrombotic event, DTE = deep thrombotic event.

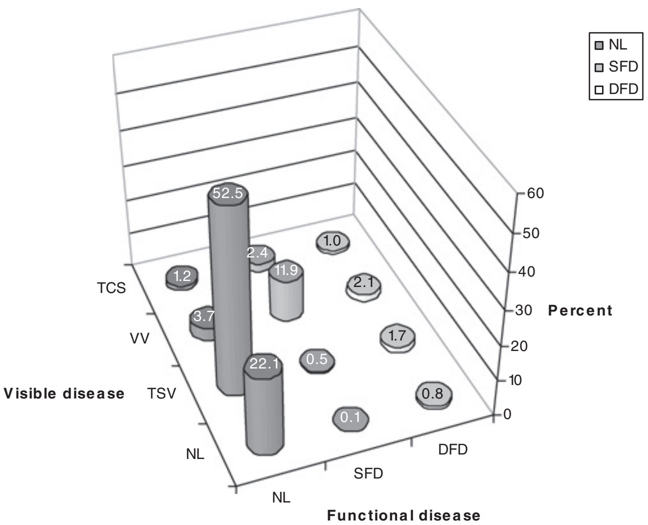

FIGURE 3.1 Visible and functional chronic venous disease in 4422 legs of 2211 persons, San Diego, California, 1994–1998.

TABLE 3.2 Prevalence of Edema, History of Superficial Thrombotic Events and History of Deep Thrombotic Events by Visible and Functional Disease, San Diego, California, 1994–1998

	NL	SFD	DFD
Edema			
NL	1.7*	0.6	6.6
TSV	1.8	14.9+	10.5+
VV	3.9	7.4+	15.6+
TCS	40.8+	30.0+	48.2+
Superficial Events			
NL	0.6*	0.0	5.3+
TSV	0.4	10.0+	0.0
VV	1.2	4.1+	1.2
TCS	0.2	4.9+	11.3+
Deep Events			
NL	1.3*	0.0	5.4
TSV	1.7	0.0	5.4+
VV	3.0	2.4	6.6+
TCS	7.7+	7.6+	26.6+

Abbreviations: NL = normal, TSV = telangiectasias and spider veins, VV = varicose veins, TCS = trophic changes, SFD = superficial functional disease, DFD = deep functional disease.
* = reference group.
+ = $p < 0.005$.

reference group are noted. Edema was closely associated with TCS. For limbs with TSV or VV, the presence of SFD or DFD greatly increased the probability of edema, as did DFD in legs visibly normal. Of legs with edema, 26% were normal functionally and had either normal or TSV visible findings, providing an estimate of the minimum number of legs on a population basis with edema of nonvenous etiology. A history of SVT was not related to visible disease in legs with normal function, but was increased similarly by both SFD and DFD. This finding is consistent with the large proportion of DFD legs that also had SFD (48%). DVT was related to both TCS and DFD, but not to VV or SFD. By far the highest prevalence of reported DVT, 25%, was in legs with both TCS and DFD. Thus although edema, SVT, and DVT were much more common in the presence of visible and/or functional disease, they also sometimes occurred in normal legs.[3]

TABLE 3.3 Significant Odds Ratios in Multiple Logistic Regression Models for Visible and Functional Venous Disease, San Diego, California, 1994–1998

	Visible disease						Functional disease			
	TSV		VV		TCS		SFD		DFD	
Covariate	M*	W*	M	W	M	W	M	W	M	W
Age (10 years)	2.3	1.2	2.5	1.5	2.3	4.5	1.8	1.6	1.4	1.2
African-American/Asian	0.3	0.4	0.2	0.4	0.2	—	—	—	—	0.5
Family History	1.8	3.0	4.2	5.8	2.9	12.0	3.5	2.1	2.6	2.0
Ankle Motility	1.3	1.2	—	1.4	—	1.4	0.8	1.3	—	0.9
Lower Limb Injury	—	—	—	—	—	—	—	—	—	1.6
CVD-Related Factors	0.1	0.3	0.1	—	—	—	0.5	0.6	0.8	0.8
Walking/Standing	—	—	1.2	1.2	1.2	1.3	1.2	1.1	—	—
Wt/Ht/BMI/Waist	—	—	—	1.4	1.3	2.0	—	1.2	1.1	—
Exercise	0.3	—	—	—	0.8	—	0.2	—	—	—
Parity/HRT Duration Yrs	—	1.1	—	1.2	—	1.3	—	1.2	—	1.2

*M = Men; w = Women; TSV = telangiectasias and spider veins; VV = varicose veins; TCS = trophic changes; SFD = superficial functional disease; DFD = deep functional disease.

RISK FACTORS FOR CPVD

We have completed an extensive analysis of risk factors for visible and functional CPVD.[8] Table 3.3 summarizes this work and shows odds ratios for significant predictors of visible and functional venous disease in our population.

Age was positively consistently related to all levels of visible and functional disease in both sexes. In comparison with non Hispanic whites (NHW), African-American Asian had less TSV and VV in both sexes, less TCS in men, and less DFD in women. Our results thus confirm that older age and NHW ethnicity are risk factors for CPVD.

Family history of venous disease based on subject recall was a risk factor for all levels of visible and functional disease. Although this finding could be biased, it is consistent with many other studies,[9,10] although not all.[11]

Ankle motility was a risk factor for visible disease SFD in women and for TSV in men. It was protective for women with DFD and men with SFD. The association of increasing laxity in connective tissue with venous disease corroborated previous research (reviewed in Reference 8). The protective associations could reflect increased ankle motility leading to decreased venous pressure by increasing pumping action.

Lower limb injury was a risk factor in women for DFD. Coughlin et al., in a case-control study, found serious lower limb trauma to be a risk factor for CVI.[11]

CVD-related factors, such as angina, PTCA, hypertension, and diastolic pressure were associated with less TSV, SFD, and DFD for men and women and less VV for men. Although some studies have found a relationship between atherosclerosis and venous disease (reviewed in Reference 8), others have not.[9] The reason for any protective effect of cardiovascular disease and hypertension on CPVD is not readily apparent, although venous vasoconstriction and microthrombosis could conceivably be involved.

Hours spent walking or standing was positively associated with VV, TCS, and SFD in men and women. Fowkes et al.[12] found that walking was a risk factor for women with venous insufficiency when age-adjusted, but less so when multiply adjusted. They found walking to be related to lessened risk of venous insufficiency in men.[12] Our data indicate that standing was a strong risk factor for venous disease in women. This is concordant with a number of studies,[9,10] and contrasts with some other studies.[12]

Weight, height, waist, and BMI, defined as weight in kg divided by height squared in meters squared, were positively associated with TCS, and DFD in men and VV, TCS, and SFD in women. Weight, waist circumference, the waist/hip ratio, and body mass index are all measures of adiposity. A number of studies have found an association of obesity with venous disease. Gourgou et al.[10] found a relationship in both men and women with VV. Our finding of increased waist circumference in men with TCS was consistent with findings that both obesity and male gender were associated with CVI and with the finding that weight was an independent risk factor for CVI in multivariate analysis (reviewed in Reference 8). In contrast, Coughlin et al. and Fowkes et al. both found that obesity was not a factor in venous insufficiency among women.[11,12] Fowkes et al. extended this finding to men as well.[12] Other studies also have found no association between obesity and venous disease.[9] However, the Edinburgh group also found that for men and women combined, persons with greater severity of varices (i.e., more segments with reflux) had higher body mass indices than those with fewer segments involved. Additionally, Fowkes et al. found that varicosities in the superficial system, but not in the deep system, were related to body mass index in women.[12]

Exercise was associated with lower rates of TSV, TCS, and SFD in men. This is concordant with the finding of

Gourgou et al. that physical activity is related to less VV.[10] During exercise the venomuscular pump is activated, which leads to a transient decrease in venous pressure, which should be protective for venous disease. This is consistent with our results in men.

HRT duration or parity was positively associated with all levels of visible and functional disease in women. Gourgou et al. found increasing VV prevalence with increasing numbers of births.[10] Coughlin et al. found that multiparity was associated with varicose veins in pregnant women.[11] Some studies have found that the changes are effected with only one pregnancy.[9] The increase of CPVD with HRT duration may indicate yet another underexamined systemic effect of HRT.

Our data indicate that age and family history were the strongest risk factors for CPVD, and neither is subject to intervention. Other significant findings on inherent factors included associations with connective tissue laxity and height. CVD-related factors were associated with lower rates of venous disease. Among volitional factors important findings were a relationship of CPVD with central adiposity, positional factors such as hours spent standing or sitting, exercise, and selected hormonal factors in women. In contrast with prior studies, we found no relationship with dietary fiber intake. In women but not men we confirmed the importance of a previous lower limb injury for DFD.

SYMPTOMS AND CPVD

The SDPS reported data for ever having any of seven symptoms of venous disease: aching, cramping, tired legs, swelling, heaviness, restless legs, and itching.[13] Aching legs was the most commonly reported venous symptom, with an overall prevalence of 17.7%. Cramping was present in 14.3% of legs, tired legs in 12.8%, and swelling in 12.2%. Heaviness and restless legs had similar prevalence at 7.5 and 7.4%. Itching was the least commonly reported symptom, affecting 5.4% of legs. With the exception of restless legs, all these symptoms increased in prevalence with increasing severity of venous functional disease (see Figure 3.2). The rate was lowest in normal legs, increased in legs with SFD, and highest in legs with DFD. These differences were statistically significant ($p < 0.01$) for all symptoms except for restless legs ($p = 0.56$). Although each symptom was more common in women than men, trends were similar in both sexes.

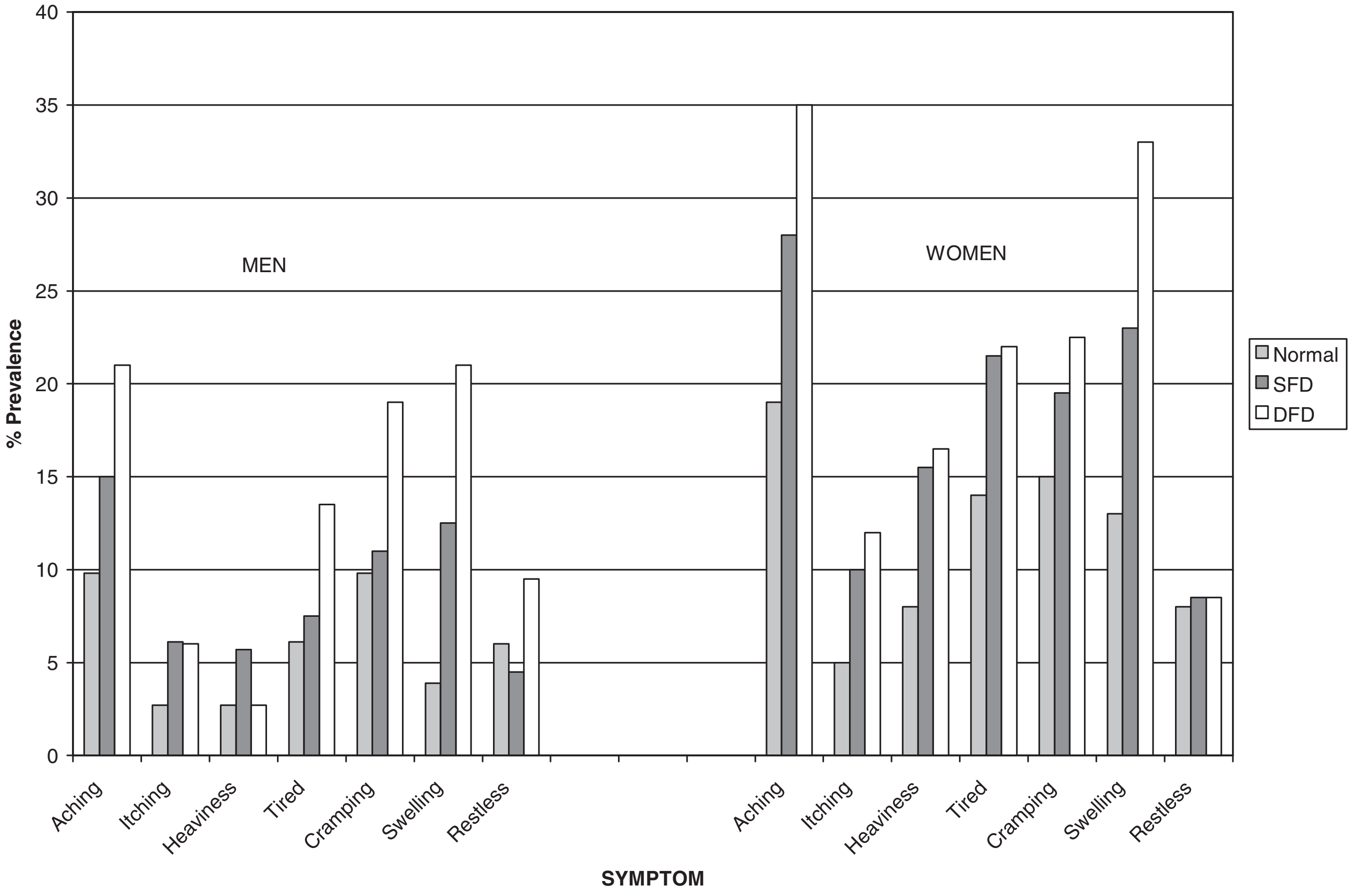

FIGURE 3.2 Symptoms by functional disease status, San Diego, California, 1994–1998.

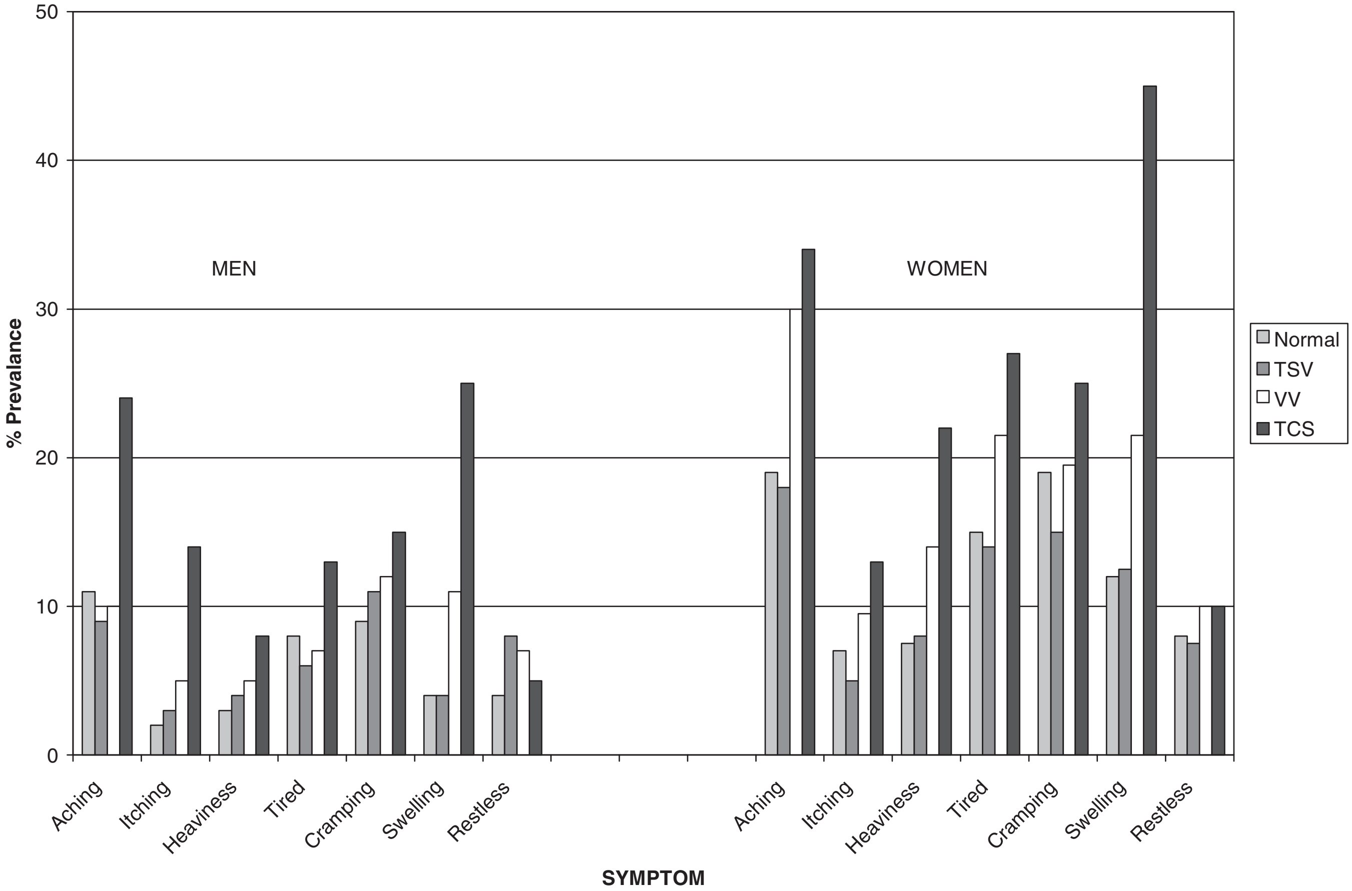

FIGURE 3.3 Symptoms by visible disease status, San Diego, California, 1994–1998.

Escalating rates of symptoms were also found across categories of visible venous disease.[13] Figure 3.3 shows the prevalence rates by symptom and visible category for each sex. Symptom prevalence in subjects with TSV, the most common category of visible disease, was only marginally greater than in normal participants. Symptoms were generally about twice as common when VV was present. Rates were further increased in the presence of TCS. Again, with the exception of restless legs ($p = 0.06$), these differences were highly statistically significant ($p < 0.01$). Similar to functional disease, symptom prevalence in association with visible disease was uniformly greater in women although trends were similar in both sexes.

SYMPTOMS BY VISIBLE AND FUNCTIONAL DISEASE

To estimate the relative importance of each symptom to the clinical picture of venous disease we evaluated the odds ratios (OR) for each symptom in each of the 12 categories of venous status formed by crossing the three categories of functional disease with the four categories of visible disease using logistic regression adjusted for age, sex, BMI, education, and racial/ethnic group (see Table 3.4). Aching (OR 2.20) and swelling (OR 2.99) were significantly associated with DFD even in subjects without visible disease. These two symptoms were significantly associated with DFD across all categories of visible disease, with the strongest association in subjects with TCS. Aching was significantly associated with VV regardless of venous functional status and was associated with TCS except in those with normal functional examinations. Itching followed a similar pattern being significantly associated with varicose veins regardless of functional status, and with TCS except in those with normal functional exams. However, the OR for itching with varicose veins and DFD was twice the level of the parallel ratio for aching (5.31 and 2.82, respectively). Swelling had associations very similar to itching for varicose veins, but was associated with much higher rates when TCS was present (ORs 11.61, 6.94, and 6.17 for swelling, itching, and aching, respectively, in subjects with DFD and TCS). Heaviness, tired legs, and cramping each had modest associations with disease in the presence of both functional and visible abnormalities. Although the symptom of restless legs was associated with disease for subjects with both DFD and

TABLE 3.4 Odds Ratios for Symptoms by Functional Disease Status Adjusted for Age, Sex, Ethnicity, Education, and Body Mass Index, San Diego California, 1994–1998

	Normal	TSV	VV	TCS
N				
Normal	1024	2519	184	58
SFD	5	22	591	117
DFD	39	87	107	55
Aching				
Normal	ref	1.11	2.05*	0.85
SFD	0.03	1.56	2.29*	3.90*
DFD	2.20*	1.93*	2.82*	6.17*
Itching				
Normal	ref	1.11	1.98*	2.63
SFD	0.04	5.88*	2.33*	4.81*
DFD	1.10	0.32	5.31*	6.94*
Heaviness				
Normal	ref	1.33	1.60	0.02
SFD	0.01	1.44	2.69*	5.68*
DFD	0.59	1.65	2.82*	5.27*
Tired				
Normal	ref	1.09	1.63*	0.42
SFD	0.01	0.30	2.07*	3.80*
DFD	1.52	1.04	2.95*	4.79*
Cramping				
Normal	ref	0.95	1.45	0.46
SFD	0.03	1.36	1.41*	1.82*
DFD	1.53	1.57	1.44	3.82*
Swelling				
Normal	ref	1.15	1.91*	5.41*
SFD	0.02	4.13*	2.31*	6.73*
DFD	2.99*	2.57*	5.82*	11.61*
Restless				
Normal	ref	1.44*	2.36*	1.13
SFD	0.03	1.50	1.64*	0.95
DFD	2.32	0.82	1.18	3.78*

*$p < 0.05$.

TSV = Telangiectasias and spider veins, VV = Varicose veins, TCS = Trophic changes, SFD = Superficial functional disease, DFD = Deep functional disease.

TCS, it did not consistently distinguish disease as rates were elevated in subjects with normal functional examinations who had either TSV or VV. In general, a combination of visible and functional findings tended to increase ORs compared with only a visible or functional finding.[13]

SYMPTOM SPECIFICITY AND CPVD

In this population-based study, aching was the most commonly reported symptom related to venous disease. However, it was relatively nonspecific as about 15% of normal subjects (assessed by either functional or visible status) reported it. Swelling was a more specific marker for prevalent disease with less than 10% of normal subjects reporting this symptom and at least a two-fold higher rate associated with functional disease or any visible disease besides TSV. Likewise, heaviness and itching were reported in legs with functional or visible findings at more than twice the rate reported in normal legs. Tired legs and cramping were also increased in legs with functional or visible findings but the contrasts with normal legs were not as strong. The joint occurrence of aching and swelling, or aching and tired legs was useful in distinguishing diseased legs.[13]

Our finding that swelling is a strong predictor is concordant with several other reports. A study of patients attending a vascular clinic found an association between vascular endothelial growth factor (VEGF) and CEAP classification, and between VEGF and swelling.[14] The Edinburgh Study, conducted in patients from clinical practices, evaluated associations by leg as in the present report. Disease was defined by the presence of superficial and deep reflux. For isolated superficial reflux, associations were found for heaviness and itching in women; there were no significant associations in men. For venous disease defined as combined superficial and deep reflux, associations were found between swelling, cramps, and itching for men, and between aching and cramps in women.[15] A study of a large employed population found swelling and nocturnal cramps to be the most common symptoms.[16] Surprisingly, in that population the strongest association was found for people with small cutaneous veins, the equivalent of TSV in our study. In a clinical population evaluated by color-flow duplex, the strongest associations were found for aching and swelling that were associated with below-knee reflux.[17]

Women were more likely to report symptoms than men. Similar results have been reported by other investigators.[16,18] This is not simply an artifact of the greater prevalence of visible disease and superficial functional disease in women[3] since it was evident on a percentage basis for each category and was also found for deep functional disease, which was more prevalent in men.

QOL AND CPVD

Despite the high prevalence of venous disease, the impact upon daily functioning and quality of life is still poorly documented. Venous disease has been considered as a cosmetic problem that might affect emotional well-being. Several studies have shown that venous disease affects selected aspects of daily functioning (reviewed in Reference 19). An ad hoc committee of the SVS/ISCVS recommended the expansion of outcome measures in studies of venous disease to include patient reported functioning and quality of life measures.[20] In their review, the ad hoc committee noted that comprehensive evaluation of venous disease must

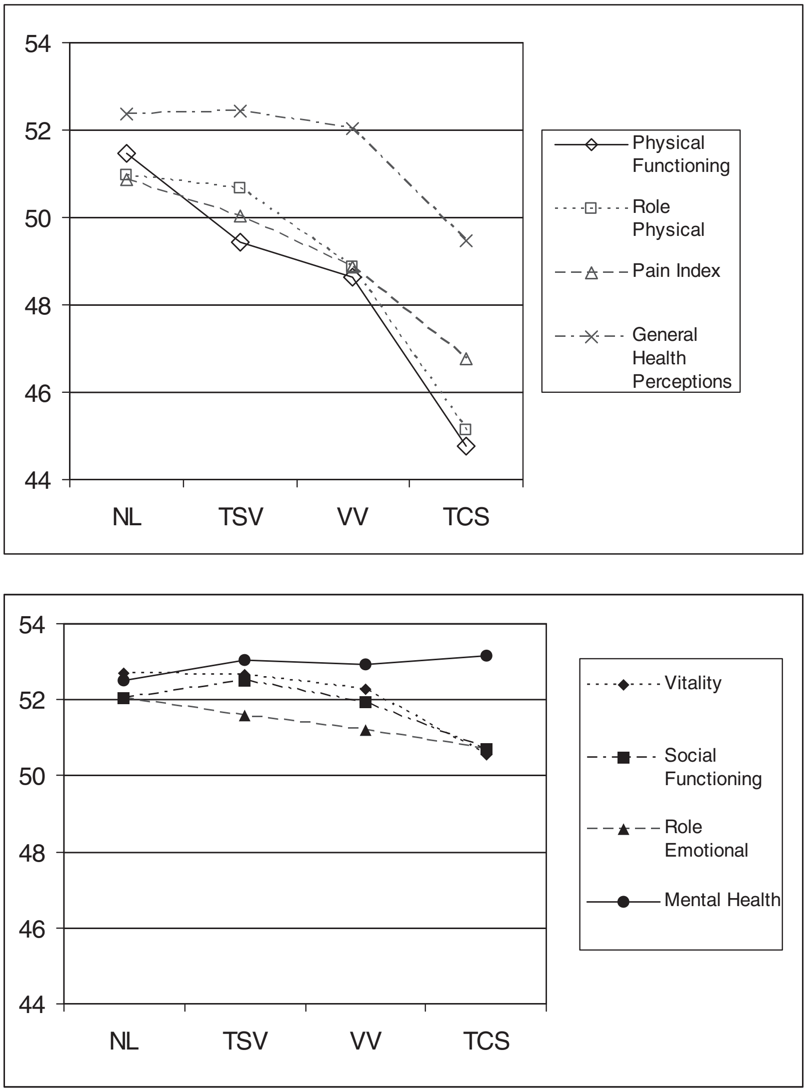

FIGURE 3.4 SF-36 scores by visible disease status for physical (top) and mental (bottom) health scores, San Diego, California, 1994–1998.

include assessment of clinical outcomes and quality of life.[20] However, only a limited number of studies have measured quality of life in patients with venous disease. At least six previous studies have used the Medical Outcomes Study 36 Item Short Form (SF-36) for patients with varicose veins. With some exceptions[21,22] patients in these studies were not well described in terms of disease status.

SF-36 AND CPVD

The SF-36 includes eight subscales. These subscales have been factor analyzed and clustered into two groups: physical and mental health.[23] Physical health components are regarded as measures of functioning, whereas mental health components are thought of as indicators of well-being. Functioning describes what people are able to do while well-being characterizes how people feel, particularly on mental health or emotional dimensions.

Scores for the four physical health components of SF-36, broken down by visible disease categories in the SDPS, are summarized in the top portion of Figure 3.4.[19] The mental health components of the SF-36 are shown in the bottom portion of the figure. The differences between visible categories of disease were highly significant with a strong linear component for the physical health subscales of the SF-36. In particular, there were strong linear effects for the Physical Functioning ($F_{1/2245}$ = 52.20, $p < 0.0001$), Role-physical ($F_{1/2245} = 41.98$, $p < 0.0001$), Pain ($F_{1/2245} = 25.43$, $p < 0.0001$), and General Health Perception scales ($F_{1/2245}$ = 8.45,

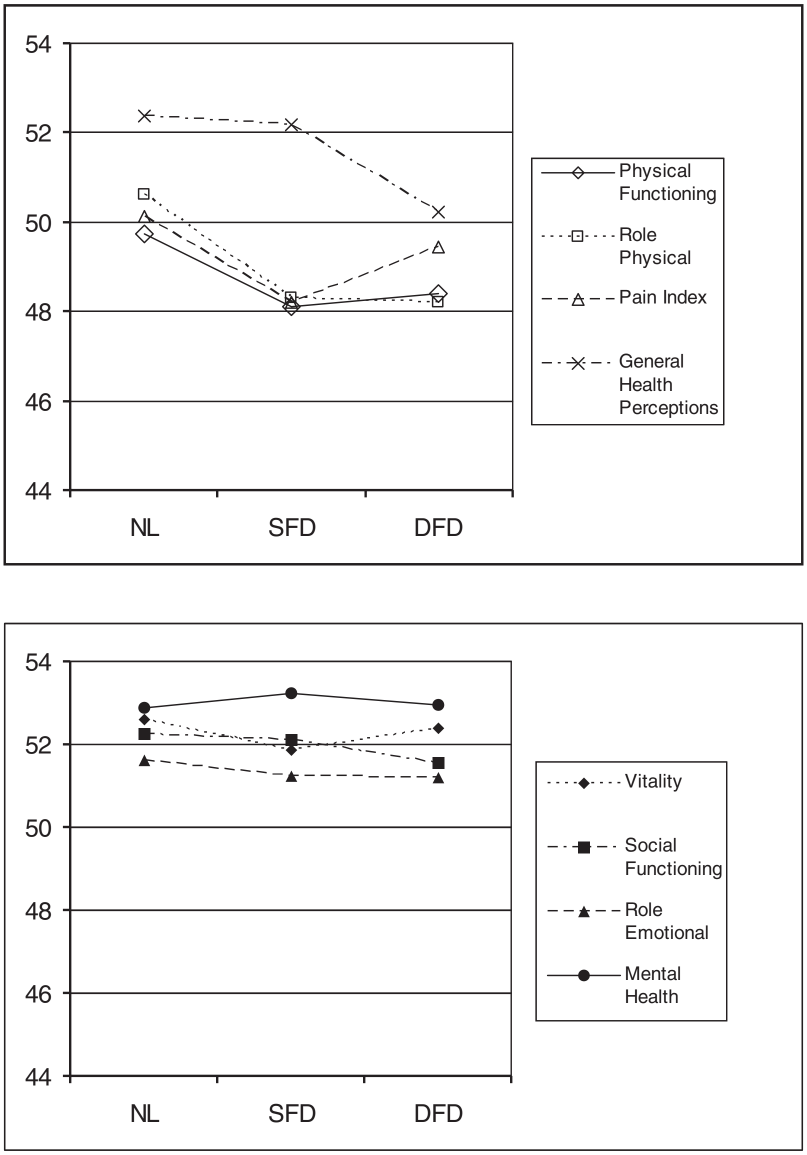

FIGURE 3.5 SF-36 scores by functional disease status for physical (top) and mental (bottom) health scores, San Diego, California, 1994–1998.

$p < 0.001$). The only significant effect for the mental health or well-being scales was for Vitality, and this effect was relatively weak in relation to the other SF-36 functional scales ($F_{1/2244} = 5.28$, $p < 0.03$).[19]

Similar trends were observed for the functional categories based on the duplex ultrasound evaluations. However, these trends were not as strong as for the visible categories (see Figure 3.5). The overall F scores were statistically significant and there were strong linear trends for all four SF-36 physical health scales (df for all tests 1/2253; Physical Functioning $F = 9.74$, $p < 0.01$; Role-Physical, $F = 23.18$, $p < 0.001$; Pain $F = 6.85$, $p < 0.01$; General Health Perceptions, $F = 9.34$, $p < 0.001$). Similar trends were not observed for any of the mental health scores and all tests of differences between groups and linear trends were nonsignificant.[19]

After adjustment for sex and ethnicity, age was significantly inversely correlated with the physical but positively correlated with the mental summary component scores (PCS, $r = -0.26$; MCS, $r = 0.18$). This suggests that older participants had lower physical health scores but slightly higher mental health scores. Men scored significantly higher on the PCS summary score than women ($p < 0.01$) and marginally higher on the MCS summary dimensions ($p < 0.10$). There were also significant differences in SF-36 summary scores by ethnicity with the Asian group scoring highest on both the PCS and MCS components. For the

MCS component, the non-Hispanic White group obtained the lowest mean score. Despite the univariate effects of age, gender, and ethnicity, adjustments for these variables did not affect the results for either visible category or functional category. This suggests that differences in quality of life are explained primarily by disease category. Ethnicity, age, and gender contribute to the prediction of quality of life, but do so independently of disease category.[19]

A final set of analyses examined the effect of visible category adjusting for functional category and the effect of functional category adjusting for visible category. These analyses focused on the PCS and MCS summary scores. Using a general linear model, we observed very strong differences in PCS by visible category ($F_{1/2211} = 35.15$, $p < .001$). However, once visible category was entered, functional category did not explain additional variance ($p = .74$). The model entering the functional categories with the visible category as a covariate still favored the visible category. These findings suggest that the visible categories explain most of the variance in the SF-36 physical component scores. In the MCS model, differences between both the visible and functional categories were nonsignificant and adjustments did not have significant effects.[19]

Evidence from this study suggests that venous disease affects the functional scales (what people can do) but does not appear to affect the well-being aspects (how people feel). Very similar results were reported in a recent European study. Kurz and colleagues also found significant gradations in SF-36 PCS scores by disease severity, but found few differences for the MCS components.[22] In addition to evidence suggesting that quality of life measures are associated with disease severity, some evidence suggests that the measures are also responsive to changes following therapeutic intervention.[24]

In summary, even modest venous disease is associated with significant limitations on the physical functioning scales of the SF-36. Venous disease did not appear to affect emotional aspects of health-related quality of life.

CONCLUSIONS

Our major findings in the SDPS for the epidemiology of CPVD are summarized as follows.

Overall Characteristics of CPVD

1. Venous disease increased with age, and NHW had more disease than Hispanics, African-Americans, or Asians.
2. TSV, VV, and SFD were more common in women, and TCS and DFD more common in men.
3. Visible and functional disease were closely linked, with 92% of legs concordant. However, since 8% of legs were discordant, the presence of one condition did not necessarily imply the other. In addition, fully one-fourth of limbs with TCS did not have functional venous disease.
4. 26.4% of legs with edema were normal functionally and without VV or TCS. This provides a population-based estimate of the proportion of edematous legs of nonvenous etiology.
5. Legs with both TCS and DFD had prevalences of edema, superficial events, and deep events of 48.2, 11.3, and 24.6%, respectively, compared with 1.7, 0.6, and 1.3% for legs visibly and functionally normal. Thus, although edema and venous thrombotic events were increased dramatically with TCS and DFD, they also occurred in their absence as well as in the absence of milder forms of CPVD.

Risk Factors for CPVD

1. The most consistent risk factor across all definitions of venous disease was family history, suggesting the importance of a genetic link.
2. Age was a strong risk factor, but somewhat more so for visible than functional disease.
3. Hormonal factors and ligamentous laxity were consistent risk factors for both visible and functional disease in women.
4. Sitting, standing, and walking were consistent risk factors for visible disease and SFD.
5. Physical anthropometric factors were risk factors in women for VV, TCS, SFD, and DFD, and for VV, TCS, and DFD in men.
6. Cardiovascular diseases tended to be inversely associated with venous disease.
7. Ethnicity associations were attenuated in multivariate analysis, although still present for TSV and VV.
8. Key risk factors for venous thrombosis, older age, obesity, and hormonal factors were also risk factors for visible and functional venous disease.
9. Other risk factors including measured heart rate; measured systolic and diastolic blood pressure; alcohol consumption; dietary fat, carbohydrate, and protein; history of diabetes; high heel use in women; history of previous or current cancer; vasectomy in men; and history of allergic disease showed at best weak associations.

Symptoms of CPVD

1. Symptoms are significantly more common in legs with visible venous disease compared to legs without, and are greater the more severe the visible disease.
2. Symptoms are significantly more common in legs with functional venous disease compared to legs

without, and are greater the more severe the functional disease.
3. The combination of visible and functional venous disease is associated with the most symptomatology, and again symptoms are a function of severity.
4. Aching is the most common symptom, and is related to both visible and functional disease.
5. Swelling shows the highest odds ratios of the seven symptoms, and is related to both visible and functional disease.
6. Nighttime restless legs and cramping are less specific symptoms for venous disease, but still show statistically significant associations.

Quality of Life in CPVD

1. QOL as defined by physical health measures is impaired by visible disease, with the impairment proportional to the severity of disease. Visible venous disease is far more than a cosmetic problem.
2. QOL as defined by physical health measures is impaired by functional disease, but much of this effect can be explained by overlap with visible disease. This is in contrast to symptoms (see earlier), where if anything, associations are somewhat stronger for functional disease.
3. QOL as defined by mental health measures did not show strong or consistent associations with either visible or functional venous disease.

Thus, CPVD is commonplace and is a major cause of morbidity in populations, including measurable effects on QOL.

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CHAPTER

4

Venous Anatomy, Physiology, and Pathophysiology

JOHN BERGAN and LUIGI PASCARELLA

In order to understand treatment of various venous disorders, it is necessary to know the normal anatomy of the venous system of the lower extremities as well as the normal functioning of its elements and the mechanisms that cause derangements in its normal functioning.

In 2001, an International Interdisciplinary Committee was designated by the Presidents of the International Union of Phlebology and the International Federation of Anatomical Associations to update the official Terminologia Anatomica, regarding the veins of the lower limbs. The relative deficiency of the official Terminologia Anatomica[1] with regard to the veins of the lower limbs was responsible for a nonuniform anatomical nomenclature in clinical literature and this caused difficulty in international exchange of information and inappropriate treatment of venous disease.[2] The Committee with the participation of Members of the Federative International Committee for Anatomical Nomenclature (FICAT) outlined a Consensus Document at a meeting held in Rome on the occasion of the 14th World Congress of the IUP. Terminological recommendations of the Committee were published[3] and these new, possibly unfamiliar, terms are used in the following exposition.

ANATOMY

The venous system in the lower extremities can be divided, for purposes of understanding, into three systems: the deep system, which parallels the tibia and femur; the superficial venous system, which resides in the superficial tissue compartment between the deep muscular fascia and the skin; and the perforating or connecting veins, which join the superficial to the deep systems. It is because these latter veins penetrate anatomic barriers, they are called perforating veins.

Although the superficial veins are the targets of most therapy, the principal return of blood flow from the lower extremities is through the deep veins. In the calf, these deep veins are paired and named for their accompanying arteries. Therefore, the anterior tibial, posterior tibial, and peroneal arteries are accompanied by their paired veins, which are interconnected. These crural veins join and form the popliteal vein. Occasionally the popliteal veins as well as more proximal deep veins are also paired like the calf veins.

As the popliteal vein ascends, it becomes the femoral vein. Formerly, this was called the superficial femoral vein, but that term has been abandoned.[3] Near the groin the femoral vein is joined by the deep femoral vein, and the two become the common femoral vein, which ascends to become the external iliac vein proximal to the inguinal ligament.

Ultrasound imaging has shown that the superficial compartment of the lower extremities consists of two compartments, one enclosing all the structures between the muscular fascia and the skin, and the other, within the superficial compartment enclosing the saphenous vein and bounded by the muscular fascia inferiorly and the superficial fascia superiorly, is termed the saphenous compartment (see Figure 4.1). The importance of this anatomic structure is underscored by its being targeted during percutaneous placement of endovenous catheters and the instillation of tumescent anesthesia.[4,5]

The main superficial veins are the great saphenous vein and the small saphenous vein. These receive many interconnecting tributaries, and these tributaries may be referred to as communicating veins. They are correctly called tributaries rather than branches of the main superficial veins. The great saphenous vein has its origin on the dorsum of the foot.

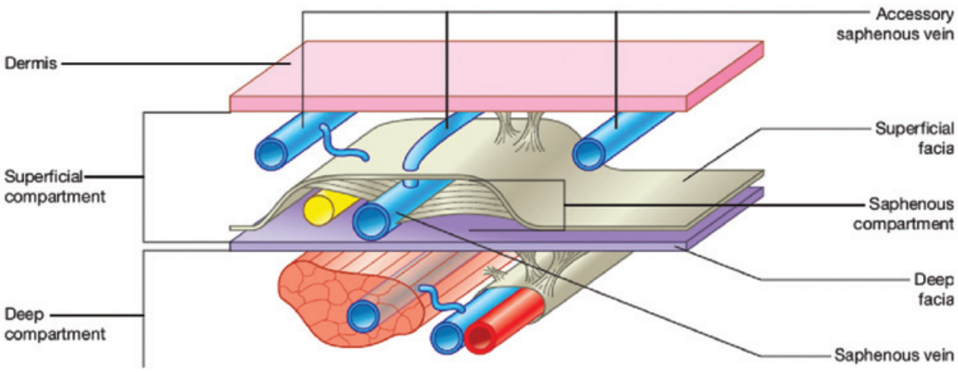

FIGURE 4.1 This diagram of the Saphenous Compartment shows its relationships with the Superficial and Deep compartments as well as the Saphenous Vein (SV) and Nerve and their relationships to the Medial, Anterior, and Lateral Accessory Saphenous Veins (ASV). (Redrawn from Reference 3.)

It ascends anterior to the medial malleolus of the ankle and further on the anteromedial aspect of the tibia. At the knee, the great saphenous vein is found in the medial aspect of the popliteal space. It then ascends through the anteromedial thigh to join the common femoral vein, just below the inguinal ligament. Throughout its course, it lies within the saphenous compartment. The small saphenous vein originates laterally from the dorsal venous arch of the foot and travels subcutaneously behind the lateral malleolus at the ankle. As it ascends in the calf, it enters the deep fascia and ascends between the heads of the gastrocnemius muscle to join the popliteal vein behind the knee (see Figure 4.2). In fact, there are many variations of the small saphenous vein as it connects both to the popliteal vein and to cranial extensions of the saphenous vein, as well as connections to the posteromedial circumflex vein (vein of Giacomini).

The third system of veins is called the perforating vein system. As indicated earlier, they connect the superficial and deep systems of veins. There is a fundamental fact, which confuses understanding of perforating veins. This relates to flow direction. Some perforating veins produce normal flow from the superficial to the deep circulation, others conduct abnormal outflow from the deep circulation to the superficial circulation. This is termed perforating vein reflux. Any of these perforating veins may demonstrate bidirectional flow (see Table 4.1).

In the leg, the principal clinically important perforating veins are on the medial aspect of the ankle and leg, and are found anatomically at approximately 6 cm intervals from the base of the heel through the upper portion of the leg. They are therefore at roughly 6, 12, 18, and 24 cm from the floor (see Figure 4.3). These medial perforating veins may become targets for treatment of severe chronic venous insufficiency. Smaller perforating veins can be found along intermuscular septa and these allow direct drainage of blood from surface veins into the deep venous system.[6] Conversely, when they are dysfunctional, they allow muscular compartment pressure to be transmitted directly to unsupported cutaneous and subcutaneous veins and venules.

TABLE 4.1 Summary of Important Changes in Nomenclature of Lower Extremity Veins

Old terminology	New terminology
Femoral Vein	Common Femoral Vein
Superficial Femoral Vein	Femoral Vein
Sural Veins	Sural Veins
	Soleal Veins
	Gastrocnemius Veins (Medial and Lateral)
Huntarian Perforator	Mid Thigh Perforator
Cockett's Perforators	Paratibial Perforator
	Posterior Tibial Perforators
May's Perforator	
Gastrocnemius Point	Intergemellar Perforator

VENOUS PHYSIOLOGY

It is estimated that 60 to 75% of the blood in the body is to be found in the veins. Of this total volume, about 80% is contained in the veins that are less than 200 µm in diameter. It is important to understand this reservoir function as it is related to the major components. The splanchnic venous circulation and the veins of the skin are richly supplied by the sympathetic nervous system fibers, but muscular veins have little or none of these. The veins in skeletal muscle, on the other hand, are responsive to catecholamines.

Although arterial pressures are generated by muscular contractions of the heart, pressures in the venous system largely are determined by gravity. In the horizontal position, pressures in the veins of the lower extremity are similar to the pressures in the abdomen, chest, and extended arm. However, with the assumption of the upright position, there

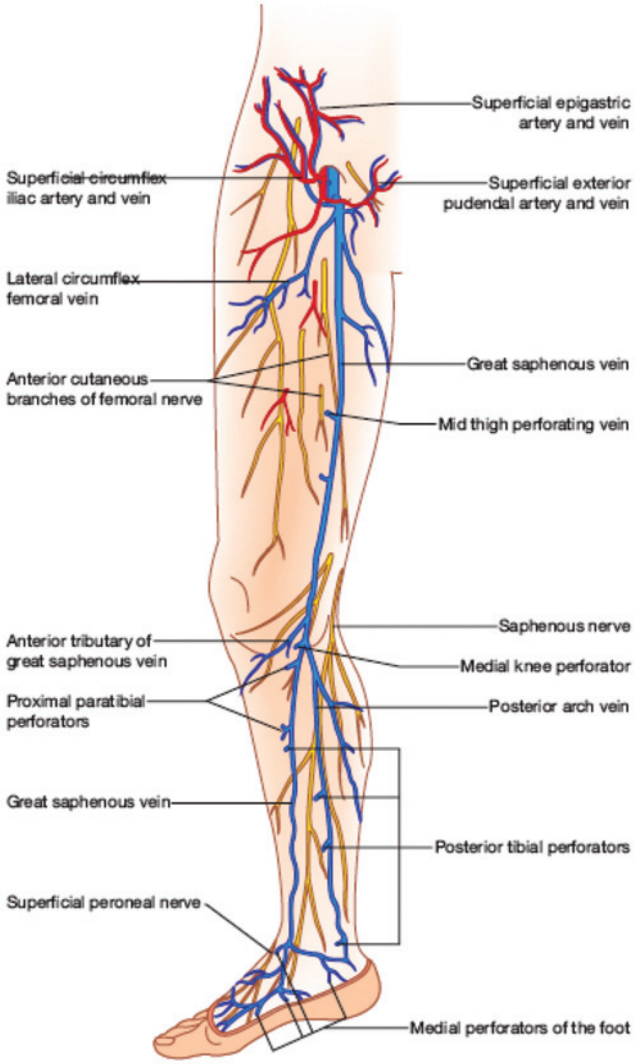

FIGURE 4.2 This diagrammatic representation of the Great Saphenous Vein emphasizes it relationship to perforating veins and the Posterior Arch Vein. (Redrawn from Mózes G, Gloviczki P, Kádár A, Carmichael SW. Chapter 2, Anatomy of the Perforating Veins in Gloviczki, P, and Bergan, JJ, eds. Atlas of Endoscopic Perforating Vein Surgery. Springer, London. 1998.)

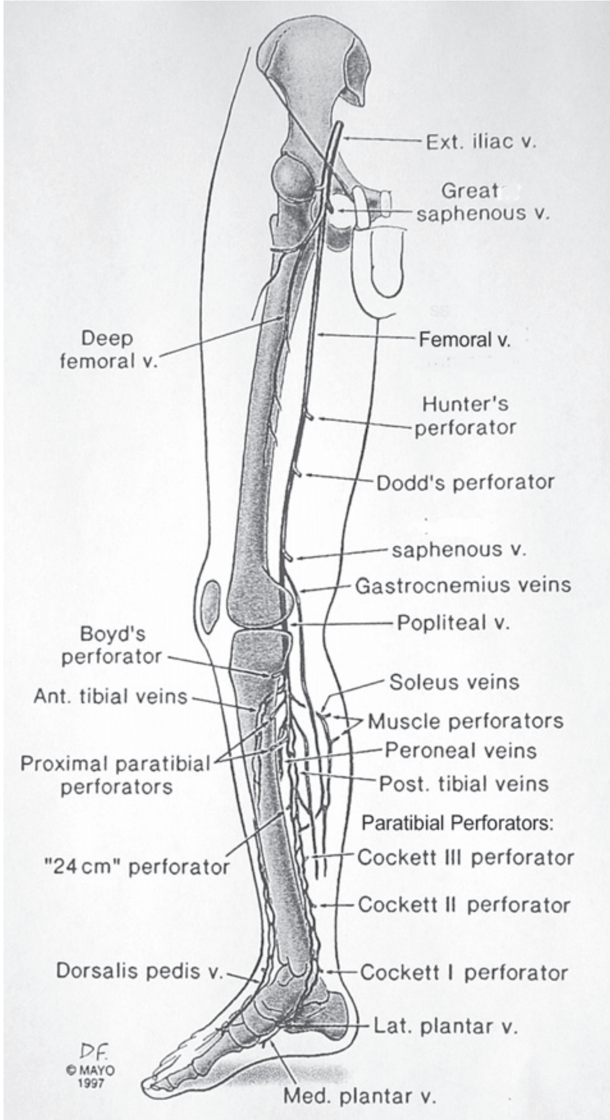

FIGURE 4.3 Deep connections of the main thigh and leg perforating veins are shown in this diagram of the deep veins of the lower extremity. (Redrawn from Mózes G, Gloviczki P, Kádár A, Carmichael SW. Chapter 2, Anatomy of the Perforating Veins in Gloviczki, P, and Bergan, JJ, eds. Atlas of Endoscopic Perforating Vein Surgery. Springer, London. 1998.)

are dramatic changes in venous pressure. The only point in which the pressure remains constant is the hydrostatic indifferent point just below the diaphragm. All pressures distal to this point are increased due to the weight of the blood column from the right atrium. When assuming the upright position, there is an accumulation of approximately 500 ml of blood in the lower extremities, largely due to reflux through the valveless vena cava and iliac veins. There is some loss of fluid into the tissues, and this is collected by the lymphatic system and returned to the venous system.

Venous valves play an important role in transporting blood from the lower extremities to the heart. In order for valve closure to occur, there must be a reversal of the normal transvalvular pressure gradient. A pressure and generated velocity flow exceeding 30 cm/second leads to valve closure. Direct observation of human venous valves has been made possible by specialized ultrasound techniques.[7] Venous flow is not in a steady state but is normally pulsatile, and venous valves undergo regular opening and closing cycles. Even when fully opened, the cross-sectional area between the leaflets is 35% smaller than that of the vein distal to the valve. Flow through the valve separates into a proximally directed jet and vortical flow into the sinus pocket proximal to the valve cusp. The vortical flow prevents stasis and ensures that all surfaces of the valve are exposed to sheer

stress. Valve closure develops when the vortical flow pressure exceeds the proximally directed jet flow.

The role of venous valves in an individual quietly standing is not well understood. Pressures in the superficial and deep veins are essentially the same during quiet standing, but as Arnoldi has found, the pressure in the deep veins is 1 mm higher, which would tend to keep the valves in the perforating veins closed.[8] Normally functioning perforating vein valves protect the skin and subcutaneous tissues from the effects of muscular contraction pressure. This muscular contraction pressure may exceed 100 to 130 mmHg.

Intuitively, the role of venous valves during muscular exercise is obvious, since their major purpose is to promote antegrade flow from superficial to deep. Volume and pressure changes in veins within the calf occur with muscular activity. In the resting position, with the foot flat on the floor, there is no flow. However, in the heel strike position, the venous plexus under the heel and plantar surface of the foot (Bejar's plexus) is emptied proximally. Blood flows from the foot and ankle into the deep veins of the calf. Then, calf contraction transports this blood into the deep veins of the thigh, and henceforth, blood flow proceeds to the pelvic veins, vena cava, and ultimately to the heart all due to the influence of lower extremity muscular contraction.[9]

PATHOPHYSIOLOGY

Abnormal functioning of the veins of the lower extremities is recognized clinically as venous dysfunction or, more commonly, venous insufficiency. Cutaneous telangiectases and subcutaneous varicose veins usually are grouped together under the title Primary Venous Insufficiency, and limbs with skin changes of hyperpigmentation, edema, and healed or open venous ulceration are termed Chronic Venous Insufficiency (CVI).

Primary Venous Insufficiency

Explanations of venous pathophysiology as published in reviews, texts, and monographs are now for the most part out of date. The new science as we now know it is incorporated in the following summary.

A dysfunctional venous system follows injury to vein walls and venous valves. This injury is largely due to inflammation, an acquired phenomenon.[10] Factors, which are not acquired, also enter into such injury. These include heredity, obesity, female gender, pregnancy, and a standing occupation in women. Vein wall injury allows the vein to elongate and dilate thus producing the visual manifestations of varicose veins. An increase in vein diameter is one cause of valve dysfunction that results in reflux. The effect of persistent reflux through axial veins is a chronic increase in distal venous pressure. This venous pressure increases as one proceeds from the inguinal ligament past the knee to the ankle. Prolonged venous hypertension initiates a cascade of pathologic events. These manifest themselves clinically as lower extremity edema, pain, itching, skin discoloration, and ulceration.[11]

The earliest signs of venous insufficiency often are elongated and dilated veins in the epidermis and dermis, called *telangiectasias*. Slightly deeper and under the skin are flat, blue-green veins of the reticular (network) system. These may become dilated and elongated as well (see Figure 4.4). And finally, still deeper but still superficial to the superficial fascia are the varicose veins themselves. All of these abnormal veins and venules have one thing in common: they are elongated, tortuous, and have dysfunctional venous valves. This implies a common cause, which is inflammation.

Chronic Venous Insufficiency

Skin changes of hyperpigmentation, scarring from previous ulceration, and active ulcerations are grouped together under the term chronic venous insufficiency (CVI). Numerous theories have been postulated regarding the cause of chronic venous insufficiency and the cause of venous ulceration.[12,13] All the theories proposed in the past century have been disproved. An example is the theory of venous stasis, first proposed in a manuscript by John Homans of Harvard in 1916.[14] It was a treatise on diagnosis and management of patients with chronic venous insufficiency, and in it, Dr. Homans coined the term "post-phlebitic syndrome" to describe the skin changes of CVI. He stated that, "Overstretching of the vein walls and destruction of the valves . . . interferes with the nutrition of the skin . . . therefore, skin which is bathed under pressure with stagnant venous blood will form permanent open sores or ulcers." That statement, like many others that describe venous conditions and their treatments, is steeped in dogma and is short of observational fact. The erroneous term stasis ulcer honors that misconception, as do the terms venous stasis disease and stasis dermatitis.

Alfred Blalock, who later initiated cardiac surgery, disproved the stasis theory by studying oxygen content from varicose veins and normal veins.[15] He pointed out that the oxygen content of the femoral vein in patients with severe chronic venous insufficiency was greater than the oxygen content of the contralateral nonaffected limb. Because oxygen content was higher, some investigators felt that arteriovenous fistulas caused venous stasis and varicose veins.[16,17] That explanation, though disproved, has some basis in fact since the entire thermal regulatory apparatus in limbs depends on the opening and closing of arteriovenous shunts. These shunts are important as they explain some terrible accidents that happen during sclerotherapy when sclerosant entering a vein is shunted into the arterial system and distributed in its normal territory.[18] Microsphere inves-

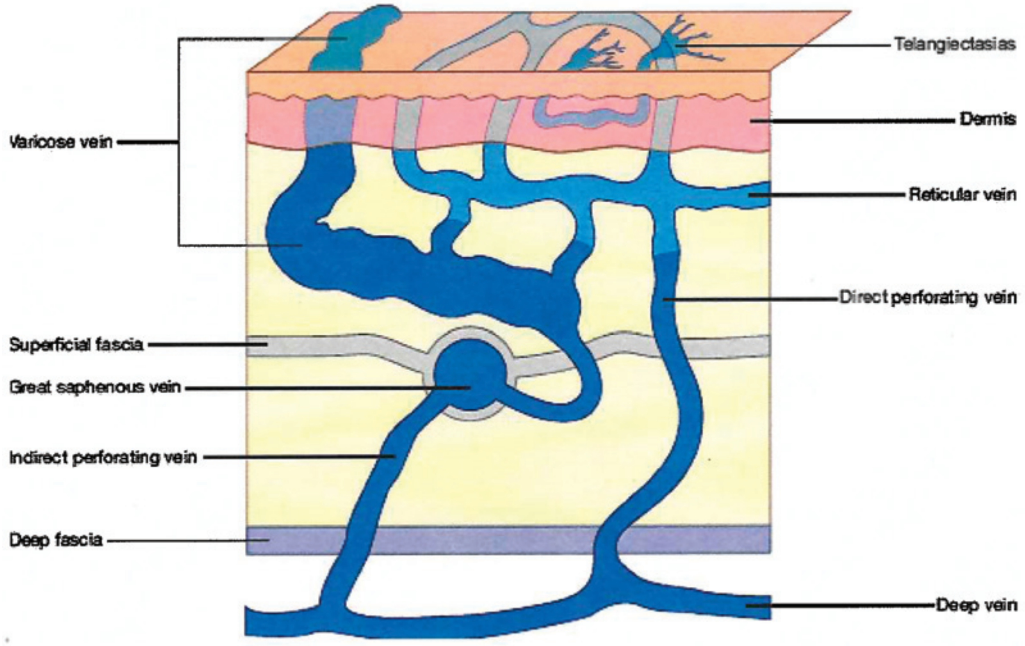

FIGURE 4.4 This cross-sectional view of the subcutaneous venous circulation shows how venous hypertension is transmitted to the unsupported veins of the dermis and subcutaneous tissues from axial veins (GSV) and the deep veins of the muscular compartments. (Redrawn from Reference 6.)

tigations have failed to show any shunting and the theory of arteriovenous communications has died despite the fact that these shunts actually exist and do open under the influence of venous hypertension.

Hypoxia and its part in causation of chronic venous insufficiency was investigated throughout the last 25 years of the twentieth century. English investigators thought that a fibrin cuff, observed histologically, blocked transport of oxygen and was responsible for skin changes of CVI at the ankles and distally.[19] That theory has been abandoned even though a true periarteriolar cuff is easily identified histologically.

The two elements that make up all the manifestations of lower extremity venous insufficiency are failure of the vein valves and vein walls and skin changes at the ankles, both of which are related to venous hypertension.[20]

Failure of Vein Walls and Valves

Our work suggests that venous hypertension causes a shear stress dependent leukocyte-endothelial interaction, which has all the manifestations of chronic inflammation.[21] These are leukocyte rolling, firm adhesion to endothelium, and subsequent migration of the cells through the endothelial barrier into parenchyma of valves and vein walls.[22] There, macrophages elaborate matrix metalloproteases, which destroy elastin and possibly collagen as well. Vein walls become stretched and elongated. Vein valves become perforated, torn, and even scarred to the point of near total absence. These changes are seen both macroscopically and angioscopically.[23] Similar changes have been produced in the experimental animal by constructing an arteriovenous fistula to mimic the venous hypertension of venous dysfunction in humans.[24]

Skin Changes

The second manifestation of chronic venous insufficiency is expressed in the skin where leukocytes also are implicated in the observed changes. There is evidence that leukocyte activation in the skin, perhaps related to venous hypertension, plays a major role in the pathophysiology of CVI. Thomas, working with Dormandy, reported that 25% fewer white cells and platelets left the dependent foot of the patients with venous hypertension. When the foot was elevated there was a significant washout of white cells but not platelets, suggesting platelet consumption within the microcirculation of the dependent foot.[25] They concluded that the decrease in white cell exodus was due to leukocyte trapping in the venous microcirculation secondary to venous hypertension. They further speculated that trapped leukocytes may become activated, resulting in release of toxic metabolites causing damage to the microcirculation and overlying skin. Apparently, the primary injury in the skin is extravasation of macromolecules and red blood cells into the dermal

interstitium. Red blood cell degradation products and interstitial protein extravasations are potent chemoattractants and represent the initial chronic inflammatory signal responsible for leukocyte recruitment.

The important observations of Dormandy's group were historically the first to implicate abnormal leukocyte activity in the pathophysiology of CVI.

The importance of leukocytes in the development of dermal skin alterations was further emphasized by Coleridge Smith and his team.[26] They obtained punch biopsies from patients with primary varicose veins, lipodermatosclerosis, and patients with lipodermatosclerosis and healed ulcers. They counted the median number of white blood cells per high power field in each group but there was no attempt to identify the types of leukocytes. In patients with primary varicose veins, lipodermatosclerosis, and healed ulceration there was a median of 6, 45, and 217 WBCs per mm^2, respectively. This demonstrated a correlation between clinical disease severity and the number of leukocytes in the dermis of patients with CVI.

The types of leukocytes involved in dermal venous stasis skin changes remain controversial. T-lymphocytes, macrophages, and mast cells have been observed on immunohistochemical and electron microscopic examinations.[27,28] The variation in types of leukocytes observed may reflect the types of patients investigated. The London group biopsied patients with erythematous and eczematous skin changes, whereas Pappas has evaluated predominantly older patients with dermal fibrosis. Patients with eczematous skin changes may have an autoimmune component to their CVI whereas patients with dermal fibrosis may have experienced pathologic alterations consistent with chronic inflammation and altered tissue remodeling Skin biopsies have shown that in liposclerotic, eczematous skin macrophages and lymphocytes were predominant in such diseased skin. Infiltration of leukocytes into the extracellular space has been documented by observing the localization of these leukocytes around capillaries and post-capillary venules. Accompanying the leukocytes is a disorganized collagen deposition. Clearly, chronic venous insufficiency of the skin and its subcutaneous tissues is a disease of chronic inflammation, again dependent upon venous hypertension.

SUMMARY AND CONCLUSIONS

Knowing the normal anatomy of the venous system of the lower extremities and the normal functioning of its elements is essential to understanding the pathologic processes of venous dysfunction. Both processes, valve and vein wall damage, and the advanced skin changes of CVI are the result of sterile inflammatory reactions. Both appear to be triggered by venous hypertension and, therefore, therapy must be directed at correcting such venous hypertension.

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CHAPTER

5

Role of Physiologic Testing in Venous Disorders

JEFFREY K. RAINES and JOSE I. ALMEIDA

Of the 25 million Americans with venous insufficiency, approximately 7 million exhibit serious symptoms such as edema, skin changes, and venous ulcers.[1] About 1 million seek formal medical advice annually and do so for symptoms of venous insufficiency. Approximately 80% of venous patients are managed conservatively with observation, leg elevation, and support stockings; the remainder are treated surgically with vein stripping or endovenous ablation. Most investigators acknowledge with the development of safe, less traumatic, and effective endovenous techniques for venous insufficiency, more individuals in the population will seek treatment, and physicians will be more inclined to move from conservative therapy to surgical therapy.

Physiologic testing is used to define deep venous thrombosis and identify, grade, and follow venous insufficiency. Since more patients will be presenting for therapy because of improved outcomes with endovenous techniques over traditional surgery, physiologic testing will take on increasing importance. For purposes of this chapter, physiologic testing includes the various devices based on plethysmographic concepts, and color flow duplex imaging. The goal of these studies is to provide accurate information describing the hemodynamic or anatomic characteristics of the patient with chronic venous insufficiency, precluding the need for invasive studies.[2]

BACKGROUND

Venous insufficiency of the lower extremity is far more frequent than venous insufficiency in any other part of the human circulation. This chapter will therefore be limited to the lower extremity. The venous system in the lower extremities is composed of three interconnected parts: the deep system, perforating (i.e., communicating) system, and superficial system. By virtue of the venous muscular pump and bicuspid/unidirectional valves, in healthy veins, blood flows toward the right side of the heart (i.e., upward) and from the superficial system to the deep system (i.e., inward).

Lower extremity muscle compartments contract during ambulation. This contraction compresses the deep veins, producing a pumping action, which propels blood upward toward the right side of the heart. This pumping action is significant; transient pressures in the deep system have been recorded as high as five atmospheres during strenuous lower extremity exertion. This pumping action secondary to ambulation has the effect of reducing pressure within the superficial system. With this in mind, it is instructive to comment on the hydrostatic pressure under which all three venous systems of the lower extremity are subjected. A fluid column has weight and can produce a pressure gradient. In an individual six feet in height, the distance from the level of the right atrium to the ankle is 120 cm and produces a hydrostatic pressure of approximately 90 mmHg.

Deep veins can withstand elevated pressure because the fascia in which they exist limits dilation. In contrast, the superficial system, surrounded by elastic skin, is constructed for low pressure; therefore, elevated pressure in the superficial system can produce dilation, elongation, and valve failure. Dilation increases the diameter of the veins and elongation causes them to be more tortuous.

Consider the following cascade of events. Because of valve failure, above-physiologic pressure develops in the superficial system. With time, nearby superficial valves begin to fail (i.e., lose their ability to direct flow in one direction). With dilation and multiple valve failure, venous blood will flow in the direction of the pressure gradient, which is downward and outward. This flow direction is

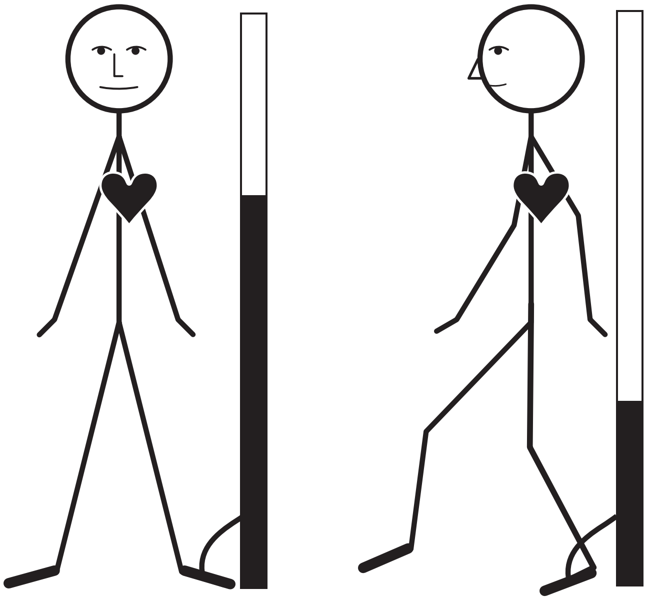


FIGURE 5.1 The stick figure on the left illustrates a normal subject erect and motionless with a venous cannulation in the left foot. Venous pressure rises to the level of the right atrium. The stick figure on the right illustrates the effect of the normal lower extremity venous pump and the unidirectional valves activated by walking or ankle flexion. The fluid column is reduced to between 50–60% of its resting value. Failure to reduce the height of the fluid column results in ambulatory venous hypertension (i.e., venous insufficiency).

directly opposite physiologic flow (i.e., upward and inward). The early result is varicose veins and telangiectasia, which are visible on the skin surface.

Early or mild venous insufficiency produces low-level pain, edema, burning, throbbing, and leg cramping. As the disease progresses patients can develop venous stasis changes that can lead to debilitating severe soft tissue ulceration. We know from hemodynamics and clinical experience, on eliminating high pressure or flow in diseased superficial venous channels, symptoms can improve dramatically.

In understanding lower extremity venous hemodynamics, the following experiment is instructive (see Figure 5.1). First, a superficial vein in the foot of a normal subject is cannulated and connected to a fluid column (sterile saline with vitamin A to add color to the column). With the subject standing erect, the fluid column will rise to the level of the right atrium. This is due to the fact that the pressure at the right atrium is near zero and therefore, the venous pressure at the cannulation site is almost entirely based on the subject's hydrostatic blood column (the subject's blood and the fluid in the column have nearly the same Specific Weight). When the subject is asked to perform sustained ankle flexion, the fluid column drops to between 50 to 60% of its resting height. This simulates walking and the reduction in superficial venous pressure secondary to the ambulatory venous pump. In subjects with venous insufficiency, the fluid column will not drop to normal levels. If a subject's fluid column falls to normal levels while occluding the superficial system, the observer knows the deep system is intact and the superficial system is incompetent. If the fluid column remains elevated with exclusion of the superficial system, the observer knows the deep system is incompetent. As will be illustrated, physiologic venous testing is based on the principles outlined in this experiment.

Although the morbidity secondary to venous insufficiency and varicose veins is significant,[3] the most devastating consequence is due to life-threatening venous thromboembolism to the lungs. In a study from the Mayo Clinic, during 14,629 person-years of follow-up, 1333 patients died. Seven-day, 30-day, and 1-year venous thromboembolism survival rates were 75%, 72%, and 64%, respectively.[4]

Two statements may summarize this section. First, the culprit in venous insufficiency syndrome is elevated pressure when limbs are dependent or ambulating. Measuring and understanding venous hemodynamics is the cornerstone of this diagnosis. Second, deep venous thromboembolism may result in venous insufficiency and may develop independently. This diagnosis is less hemodynamically oriented and more focused on sonographic visualization of thrombi.

PLETHYSMOGRAPHY

Plethysmographs are devices that measure volume change. Over the last 50 years plethysmographs have been developed and used clinically that employ completely different principles. Descriptions of four plethysmographs are given next.

Impedance Plethysmograph (IPG)

This device is based on a fundamental principle of electronics, which states that voltage (V) across a localized segment is equal to the impedance (Z) (i.e., resistance, inertance, and capacitance) of the segment times the current (I) flowing through the segment of interest ($V = Z \times I$). It is possible to isolate a portion of a limb (thigh, calf, lower leg, etc.) and subject the limb segment to a standard and known current while measuring the voltage across the segment. In this setting the measured voltage is proportional to the impedance of the segment. Most materials demonstrate impedance. Therefore, blood, subcutaneous tissue, and even bone have impedance. If we make the assumptions that impedance of a limb segment can be measured accurately, blood volume is the only significant variable with time, and that arterial blood volume change is electrically filtered or small compared to venous blood volume measured, then voltage is proportional to venous volume in the segment.

In practice the operator places circular electrodes around the segment of interest, generally the proximal calf, and connects the electrodes to the electrical console. The subject is asked to perform a series of maneuvers, and outputs from the device are recorded. The maneuvers and outputs are similar for all plethysmographs described in this chapter and are given later. This method has been used with success by some investigators in the assessment of DVT and venous insufficiency.[5,6] However, there are a number of factors that limit its accuracy. First, the set-up is tedious and must be done with care. Second, the coupling of the device to the skin surface is important and unfortunately variable between measurements and during examinations. Third, the signal-to-noise-ratio between the real physiologic change and the baseline error is low. For these reasons and the fact that more clinically oriented plethysmographic methods have been developed, the technique is not used routinely.

Strain-Gauge Plethysmograph (SGP)

This device measures circumference of a selected limb segment. Circumference is related to segment cross-sectional area, and cross-sectional area multiplied by length is volume. In using SGP the following assumptions are made. First, blood volume is the only significant variable with time, and second, arterial blood volume change is small compared to venous blood volume changes.

The device is constructed using a small hollow elastic tube, mercury, and an electrical circuit capable of measuring voltage across the tubing length. The hollow flexible tube is filled with mercury, which conducts electricity well.

The tube containing the mercury is carefully placed around the limb segment of interest and connected to the electric circuit. The subject is asked to perform a series of maneuvers, and outputs from the device are recorded. The maneuvers and outputs are similar for all plethysmographs described in this chapter and are given later. As the limb segment circumference is changed secondary to venous blood volume, the length of elastic tube changes. The voltage is measured and displayed by the circuit. By measuring circumference as a function of time, venous blood volume as a function of time may be measured.[7,8]

This technique has a number of drawbacks. First, the instrumentation is difficult to construct. Second, the assumption that circumference measured over a very small slice of the limb segment represents volume change in the segment is often not true. Third, as in the case of IPG, the signal-to-noise-ratio is low. Along with IPG, this method is rarely used in contemporary clinical settings.

Photoplethysmograph (PPG)

Photoplethysmographs are not true plethysmographs because the measure they provide is qualitative and cannot be used to determine volume. Despite this limitation, PPG is used in many clinics to assess venous insufficiency.[9,10] The device measures phenomenon limited to the microvasculature of the cutaneous skin. PPG instrumentation includes a surface transducer, which is taped to the lower leg just above the medial malleolus and connected to an electrical circuit. The electrical circuit excites the transducer and records and interprets the returning signal.

The PPG transducer is designed with an infrared light emitting diode and a photosensor. The transducer transmits light to the skin, which is both scattered and absorbed by the tissue in the illuminated field. Blood is more opaque than surrounding tissue and therefore attenuates the reflected signal more than other tissue in the field. The intensity of reflected light is reduced with more blood in the field. If the electrical circuit filters the higher frequency arterial pulsations it is possible to register a signal, which qualitatively corresponds to venous volume in the segment of interest. PPG therefore is able to detect changes in venous filling secondary to various patient maneuvers, which will be described later. PPG has found a role in the clinical assessment of venous insufficiency.

Air Plethysmograph (APG)

Properly designed air plethysmographs more accurately measure true volume than IPG, SGP, or PPG and are easier to use in the clinical setting.[11–14] The instrumentation is characterized by three major components. The first component is the transducer, which is a form of closed air bladder used to surround the limb segment of interest. The second component is a pressure sensor, which can accurately measure the pressure in the air bladder as a function of time. The third component is the electrical circuit necessary to control the pressure sensor and display the measured results.

As mentioned earlier, use of the APG is relatively simple. The air bladders are generally self-contained units similar to standard blood pressure cuffs and are designed for specific limb segments. The connection to the console generally is limited to a single rubber tube with connector. With the air bladder surrounding the limb segment of interest, any change in volume in the limb segment will cause the pressure within the bladder to change. For example if limb volume increases the bladder volume will decrease. Since the bladder is a closed system, this will cause the bladder pressure to increase. Accurate APG carefully correlates bladder state (i.e., mean bladder pressure and volume), instantaneous change in bladder pressure, and limb volume change. APG is able to detect changes in venous limb volume secondary to various patient maneuvers. The maneuvers and outputs are similar for all plethysmographs described in this chapter and are given later. APG is used in the clinical assessment of venous insufficiency and DVT.

Definition of Parameters and Maneuvers Used in Generic Plethysmography for Venous Insufficiency

Venous insufficiency causes the three venous systems in the lower extremity to misdirect venous blood volume. Therefore, the goal of this testing is to characterize misdirection of venous blood volume, if present.

Our test subject is placed in the supine position. This will lower venous pressure in the lower extremities to a value only slightly above right atrial pressure (~0 mmHg). Using a plethysmograph an operator can obtain a baseline volume in the segment of interest. When the subject is placed in the erect position, lower extremity venous pressure increases due to the hydrostatic column of blood extending from the right atrium to the segment of interest. Since veins are compliant (i.e., increase volume with increased internal pressure), vein blood volume in the segment of interest increases. This volume increase is displayed on a graph from which measurements may be taken. The Y-axis is volume, and the X-axis is time. Since all measurements are either times or ratios, the Y-axis is not required to be strictly calibrated as volume. However, its display on the graph must correlate with volume change (see Figure 5.2).

The measurement between the supine baseline volume and the erect volume plateau is known as the *Venous Volume (VV)*. From this same curve the operator can determine the *Venous Refilling Time (VRT)*. This is the time measured from when the baseline volume begins to increase to its plateau. With the subject in the erect position, the operator instructs the subject to perform a single brisk ankle flexion. This will produce a momentary reduction in Y-axis volume. This change in volume is called the *Ejection Volume (EV)*. To calculate the *Ejection Fraction (EF)*, the operator divides EV by VV. The subject is then instructed to perform 10 brisk ankle flexions. This will produce a reduction in Y-axis volume, which will be larger than the volume reduction experienced with one flexion. This allows the operator to measure *Residual Volume (RV)*. This is defined as the difference between the volume after 10 flexions and the baseline volume. Finally, the operator can calculate the *Residual Volume Fraction (RVF)* by dividing RV by VV.[15–17]

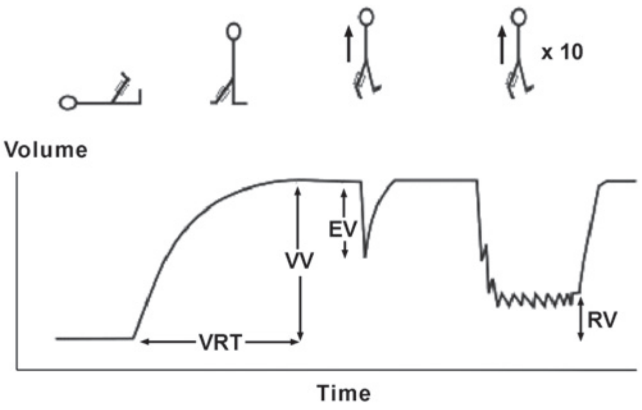


FIGURE 5.2 This figure illustrates parameter definitions and maneuvers used generically in plethysmographic studies for venous insufficiency.

Simplified Diagnostic Criteria for Venous Insufficiency

These criteria may be applied to any plethysmograph. The only restriction is that the volume measurements be taken accurately. In order to simplify the diagnostic criteria for venous phlethysmographic studies we have focused on three parameters. The first is *Venous Refilling Time (VRT)*. In patients with significant venous insufficiency, venous refilling develops secondary to venous reflux and clearly reduces the time necessary to complete the process. If VRT is >20 seconds, the limb is not demonstrating significant reflux. If VRT is <20 seconds, the diagnosis of venous reflux should be considered.[17] This should be taken in light of the finding that subjects with VRT <10 seconds very often present with venous ulceration.[18] The second parameter is *Ejection Fraction (EF)*. In patients with deep or superficial venous insufficiency or deep venous thrombosis, EF is reduced. If EF is >60% the limb is presenting with normal venous hemodynamics. For superficial venous insufficiency the average EF is 50%. Average EF is reduced to 40% in subjects with deep venous insufficiency and 35% in deep venous obstruction. The third measurement is *Residual Volume Fraction (RVF)*. If RVF is elevated, the limb is demonstrating venous ambulatory hypertension. A normal value for RVF is <35%. Subjects with RVF >35% should be evaluated further for venous disease.[17]

Deep Venous Thrombosis—Examination by Plethysmography

The four plethysmographs just described have been used for the identification and monitoring of DVT. For purposes of this text a generic procedure for DVT will be described.

Deep venous thrombosis is a life-threatening disease; for that reason alone accurate diagnosis and therapy are essential. The deep venous system is not only a conduit for returning blood to the right side of the heart; it is also a storage or capacitant system. This means its volume changes rapidly as pressure within the deep system changes. If one examines a vein at low pressure the walls are nearly fully collapsed and only a small flow channel is present. It takes very little increase in internal fluid pressure to expand the flow channel of a vein. Finally, if there is obstruction in a segment of deep vein, despite rich venous collateral channels, venous

pressure distal to the obstruction will increase. Examination by plethysmograph makes use of these two principles (i.e., volume change with increased pressure and resistance).

Typically a plethysmograph transducer is placed at the calf or distal thigh with the patient lying supine on a table. In the case of APG the transducer is an air bladder inflated to 5 mmHg; in the case of PPG the transducer is a light emitting diode. Proximal to the transducer a method of rapidly occluding the deep system must be used. For all transducers this can be a thigh cuff inflated rapidly by hand bulb or automatic inflator.

With the transducer recording a stable venous signal at 5 mm/second chart speed, the pressure in the proximal occluding cuff is rapidly elevated to 50 mmHg. The transducer is measuring absolute levels of volume.

With the increased pressure in the proximal cuff, venous blood in the deep system cannot pass under the cuff until the venous pressure reaches approximately occluding cuff pressure. This increase in venous pressure (i.e., pooling) develops because the proximal cuff does not obstruct the arterial inflow. After about 20 to 40 seconds, pressure in the distal venous system reaches the pressure in the occluding cuff and venous volume reaches a plateau. Once the plateau has been reached, the operator rapidly releases the pressure in the occluding cuff. The pooled venous blood can then return to the right side of the heart via the larger veins upstream. Two measures of venous hemodynamics are taken during this test. First, there is the volume increase from the baseline to the plateau. This is known as Segmental Venous Capacitance (SVC) and represents the blood storage capacity of the segment vein. This generally is quoted in mm of deflection or ml if the system is calibrated to volume. The second measurement is the slope of the volume-time curve immediately after the pressure in the occluding cuff is released. This is known as Maximum Venous Outflow (MVO) and represents resistance to blood flow in the deep system. This may be quoted in mm of deflection/second or ml/second if the system is calibrated to volume. The next two sections define the diagnostic use of these parameters.

Segmental Venous Capacitance (SVC)

With experience, vascular technologists and physicians are able to identify a normal range of SVC with their specific plethysmographic equipment. With the subject supine, normal veins have significant capacitance. If proximal deep venous obstruction is present, pressure distal to the obstruction increases and SVC is markedly reduced. Therefore, if SVC reduces more than 25% when compared to normal levels, venous abnormality is suggested.[11] It is recommended that SVC always be measured bilaterally. In the case of unilateral disease, the normal limb can serve as a control, which increases both sensitivity and specificity.

Maximum Venous Outflow (MVO)

As in the case of SVC, vascular technologists and physicians are able to identify a normal range of MVO with their specific plethysmographic equipment. Normal veins exhibit a very rapid decrease in volume on deflation of the occluding cuff. When deep system resistance is increased due to deep venous obstruction, the reduction in MVO is dramatic. Again, in the case of unilateral disease, the normal limb can serve as a control. A difference in MVO between limbs of 25% is abnormal.[11]

When Continuous-wave Venous Doppler measurements, SVC, and MVO are performed as a diagnostic package, sensitivity and specificity of the combined testing reach 85%, respectively.[11] It should be acknowledged Duplex Venous Doppler Ultrasonic Imaging, which requires more expensive equipment, clearly demonstrates a higher sensitivity and specificity. Further, ultrasound is able to more accurately localize obstruction and age thrombus. For this reason, plethysmographic methods have limited diagnostic use. There is one area in venous disease where SVC and MVO provide unique and important information. This is in the determination of venous collaterization following a DVT. Patients that normalize SVC and MVO rapidly have an improved prognosis when compared to subjects in which normalization is prolonged.

CONTINUOUS-WAVE VENOUS DOPPLER (CW DOPPLER)

CW Doppler instruments are widely available, relatively inexpensive, and used extensively to rapidly investigate the peripheral vascular system. CW Doppler measurements can be used independently, or as mentioned earlier, combined with measurements from a plethysmograph. The purpose of this section is to outline how CW Doppler is used to facilitate the diagnosis of venous insufficiency of the deep system, specifically deep vein reflux and deep venous thrombosis.

Deep Venous Thrombosis

Strandness and Baker introduced CW Doppler in the 1960s.[19] Its initial application was peripheral arterial assessment. With the development of additional maneuvers the instrumentation was applied first to the diagnosis of DVT and later to deep vein insufficiency.

We recommend that the subject be studied on a flat examining table in which the lower extremities may be placed in the dependent position at approximately 15 degrees. This slight angle dilates the deep system, which makes the identification of veins easier and improves the velocity signals. We recommend that target veins include the common femoral vein at the inguinal ligament, popliteal vein at the

popliteal fossa, and the posterior tibial vein just behind the medial malleolus.

With the pencil-like probe positioned toward the venous flow and at 60 degrees to the flow streamline, the target velocity is optimized. The fact that a velocity is identified means the vein is patent at the target level; this is the first of three major diagnostic criteria. The second diagnostic criterion is associated with the spontaneous and phasic nature of the signal. When veins are not obstructed proximal to the target vein, the local pressure is low and local velocity changes as a function of respiration. Low-pressure veins collapse and local velocity often is reduced to zero shortly after inspiration. This is due to the fact that when the diaphragm moves down on inspiration, pressure in the closed abdominal cavity increases and collapses veins at low pressure. With proximal obstruction this phasic velocity is disturbed in the sense that velocity is no longer phasic with respiration and in fact may be continuous. The third criterion is associated with velocity response secondary to distal compression. When veins are unobstructed proximal to the target and compression is performed distally, the local velocity will increase in response to compression. In a high resistance proximal venous system, distal compression will not evoke increased velocity.

If a subject demonstrates at the femoral, popliteal, and posterior tibial veins good velocity signals that are phasic with respiration and augment with distal compression, the chance of DVT involving the iliac, common femoral, femoral, or popliteal veins is very low. DVT limited to the calf veins is more problematic due to vein duplication at this level. As mentioned earlier, when CW Doppler is combined with venous plethysmography (SVC and MVO) the sensitivity and specificity of the combined package is 85%, respectively.[11]

Venous Insufficiency

The main use of CW Doppler in venous insufficiency is in assessing reflux in the major deep veins of the lower extremity (common femoral, femoral, and popliteal veins). This procedure is most effectively performed with the subject standing. To the extent possible, weight should be shifted to the contralateral leg. A bidirectional CW Doppler with a stereo audio signal and printout is recommended. For venous work an ultrasound frequency range of 5 to 7 MHz is suggested. As a quick review, the pencil-like probe of the CW Doppler should be aligned toward the flow and at an angle of approximately 60 degrees to the anticipated flow streamline. Unlike Duplex Ultrasound, with CW Doppler the exact path of the target vein is not well defined. Therefore, in practice the operator will have to adjust the probe angle manually to obtain the maximum signal (audio level and velocity level). The concept is quite simple; target veins are assessed for reversal of flow velocity after rapid manual limb compression and release. The more reversal, the more reflux. In terms of diagnostic criteria, a normal vein demonstrates no evidence of reflux using this technique. Flow reversal can be assessed both by audio signal and by examination of velocity versus time printouts.[17]

ASSESSMENT OF THE DEEP AND SUPERFICIAL VENOUS SYSTEMS USING DUPLEX ULTRASOUND

The two sections preceding this text described pure physiologic measures. This section will focus on the combination of physiologic and imaging measures. Further, Duplex Ultrasound has become the “gold standard” in the diagnosis of both deep venous thrombosis and venous insufficiency. The method is so pervasive that it has replaced in most venous centers the use of venous plethysmographs and CW Dopplers. It also should be stated that the accuracy, speed, and cost of this procedure to diagnose deep venous thrombosis have been so attractive that venography is rarely indicated or necessary.

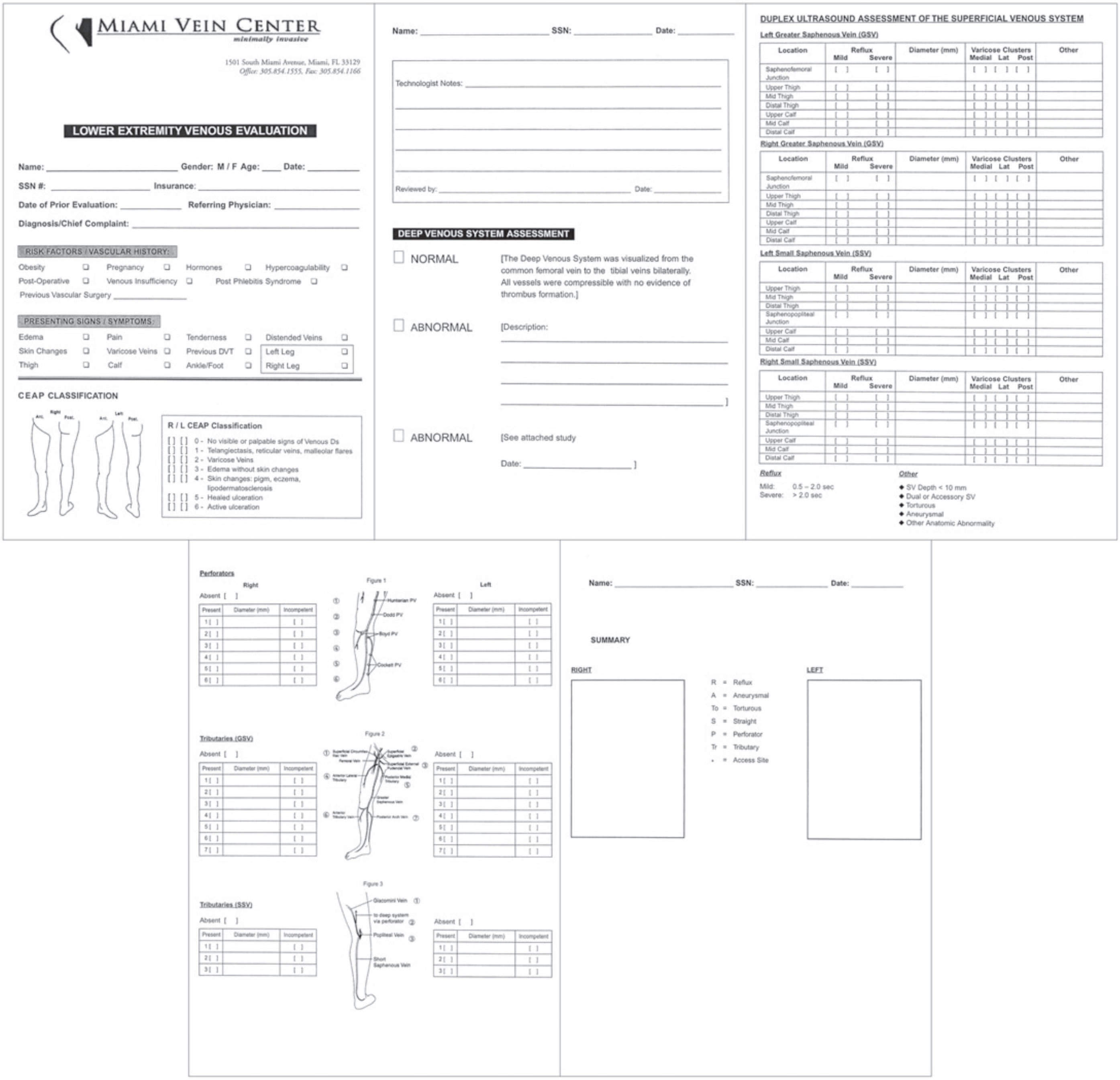
Power Color Pulsed-Wave Doppler and High-Resolution B-mode Imaging characterize state-of-the-art Duplex Ultrasound. Descriptions of these devices are found elsewhere in this book and are commonplace in medical literature. The remaining sections describe our approach to the assessment of the deep and superficial systems using duplex ultrasound. This essentially follows the worksheet and procedures our technologists use at the Miami Vein Center (see Figure 5.3).

Risk Factors, Vascular History, Presenting Signs and Symptoms, and CEAP Classification

In addition to demographic data we suggest risk factors and associated history be recorded. This includes parameters like obesity, pregnancy, hormone use, and hypercoagulability. Also recorded for each leg are presenting signs and symptoms like edema, pain/tenderness, skin changes, varicose veins, and previous DVT. We have found the CEAP Classification to be helpful in describing degree of disease and in developing management plans.[20]

Deep Venous System Assessment

We recommend that the subject be studied on a flat examining table in which the lower extremities may be placed in the dependent position at approximately 15 degrees. This slight angle dilates the deep system, which makes the identification of veins easier and improves the velocity signals. We recommend deep vein interrogation from the level of the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LOWER EXTREMITY VENOUS EVALUATION

Name: ______ Gender: M / F Age: ____ Date: ______
SSN #: ______ Insurance: ______
Date of Prior Evaluation: ______ Referring Physician: ______
Diagnosis/Chief Complaint: ______

RISK FACTORS / VASCULAR HISTORY:
Obesity ❑ Pregnancy ❑ Hormones ❑ Hypercoagulability ❑
Post-Operative ❑ Venous Insufficiency ❑ Post Phlebitis Syndrome ❑
Previous Vascular Surgery ______

PRESENTING SIGNS / SYMPTOMS:
Edema ❑ Pain ❑ Tenderness ❑ Distended Veins ❑
Skin Changes ❑ Varicose Veins ❑ Previous DVT ❑ Left Leg ❑
Thigh ❑ Calf ❑ Ankle/Foot ❑ Right Leg ❑

CEAP CLASSIFICATION

R / L CEAP Classification
[ ] [ ] 0 - No visible or palpable signs of Venous Ds
[ ] [ ] 1 - Telangiectasis, reticular veins, malleolar flares
[ ] [ ] 2 - Varicose Veins
[ ] [ ] 3 - Edema without skin changes
[ ] [ ] 4 - Skin changes: pigm, eczema, lipodermatosclerosis
[ ] [ ] 5 - Healed ulceration
[ ] [ ] 6 - Active ulceration

Name: ______ SSN: ______ Date: ______

Technologist Notes: ______
Reviewed by: ______ Date: ______

DEEP VENOUS SYSTEM ASSESSMENT
☐ NORMAL [The Deep Venous System was visualized from the common femoral vein to the tibial veins bilaterally. All vessels were compressible with no evidence of thrombus formation.]
☐ ABNORMAL [Description: ______]
☐ ABNORMAL [See attached study Date: ______]

DUPLEX ULTRASOUND ASSESSMENT OF THE SUPERFICIAL VENOUS SYSTEM

Left Greater Saphenous Vein (GSV)

Location	Reflux Mild	Reflux Severe	Diameter (mm)	Varicose Clusters Medial Lat Post	Other
Saphenofemoral Junction	[ ]	[ ]		[ ] [ ] [ ]	
Upper Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Mid Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Distal Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Upper Calf	[ ]	[ ]		[ ] [ ] [ ]	
Mid Calf	[ ]	[ ]		[ ] [ ] [ ]	
Distal Calf	[ ]	[ ]		[ ] [ ] [ ]	

Right Greater Saphenous Vein (GSV)

Location	Reflux Mild	Reflux Severe	Diameter (mm)	Varicose Clusters Medial Lat Post	Other
Saphenofemoral Junction	[ ]	[ ]		[ ] [ ] [ ]	
Upper Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Mid Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Distal Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Upper Calf	[ ]	[ ]		[ ] [ ] [ ]	
Mid Calf	[ ]	[ ]		[ ] [ ] [ ]	
Distal Calf	[ ]	[ ]		[ ] [ ] [ ]	

Left Small Saphenous Vein (SSV)

Location	Reflux Mild	Reflux Severe	Diameter (mm)	Varicose Clusters Medial Lat Post	Other
Upper Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Mid Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Distal Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Saphenopopliteal Junction	[ ]	[ ]		[ ] [ ] [ ]	
Upper Calf	[ ]	[ ]		[ ] [ ] [ ]	
Mid Calf	[ ]	[ ]		[ ] [ ] [ ]	
Distal Calf	[ ]	[ ]		[ ] [ ] [ ]	

Right Small Saphenous Vein (SSV)

Location	Reflux Mild	Reflux Severe	Diameter (mm)	Varicose Clusters Medial Lat Post	Other
Upper Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Mid Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Distal Thigh	[ ]	[ ]		[ ] [ ] [ ]	
Saphenopopliteal Junction	[ ]	[ ]		[ ] [ ] [ ]	
Upper Calf	[ ]	[ ]		[ ] [ ] [ ]	
Mid Calf	[ ]	[ ]		[ ] [ ] [ ]	
Distal Calf	[ ]	[ ]		[ ] [ ] [ ]	

Reflux
Mild: 0.5 – 2.0 sec
Severe: > 2.0 sec

Other
◆ SV Depth < 10 mm
◆ Dual or Accessory SV
◆ Torturous
◆ Aneurysmal
◆ Other Anatomic Abnormality

Perforators

Right Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]
4[ ]		[ ]
5[ ]		[ ]
6[ ]		[ ]

Figure 1
Hunterian PV
Dodd PV
Boyd PV
Cockett PV

Left Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]
4[ ]		[ ]
5[ ]		[ ]
6[ ]		[ ]

Tributaries (GSV)

Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]
4[ ]		[ ]
5[ ]		[ ]
6[ ]		[ ]
7[ ]		[ ]

Figure 2

Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]
4[ ]		[ ]
5[ ]		[ ]
6[ ]		[ ]
7[ ]		[ ]

Tributaries (SSV)

Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]

Figure 3
Giacomini Vein
to deep system via perforator
Popliteal Vein
Short Saphenous Vein

Absent [ ]

Present	Diameter (mm)	Incompetent
1[ ]		[ ]
2[ ]		[ ]
3[ ]		[ ]

Name: ______ SSN: ______ Date: ______

SUMMARY

RIGHT LEFT

R = Reflux
A = Aneurysmal
To = Torturous
S = Straight
P = Perforator
Tr = Tributary
• = Access Site

FIGURE 5.3 Worksheets used by vascular technologists at the Miami Vein Center in the assessment of the lower extremity deep and superficial venous systems.

inguinal ligament to the distal calf. This includes the common femoral, popliteal, and tibial veins. In special cases the deep femoral vein may be added to this list. Effective imaging requires the technologist have a comprehensive understanding of venous and arterial anatomy.

The evaluation begins by obtaining a B-mode image of the structures at the level of the inguinal ligament. In a single transverse view it is generally possible to see the common femoral vein, common femoral artery, and great saphenous vein. In Florida, we refer to this image as the "Mickey Mouse Image" because of the similarity to the Disney character. We have found keeping the lateral (arterial) structures on the left side of the screen for both the right and left leg to be helpful. This requires that the technologist rotate the

linear array probe 180 degrees when moving from the right to the left leg. The marker on the probe should be oriented to the lateral aspect of the leg. With this orientation, Mickey's face is the common femoral vein and is the larger and lower of the three structures. The common femoral artery is Mickey's right ear and the great saphenous vein (GSV) is Mickey's left ear. As the probe is moved distally, the GSV will disappear, and the common femoral artery will divide into the superficial femoral artery and the deep femoral artery. As the probe continues distally the technologist should focus on keeping the superficial femoral artery and the femoral vein in clear view. The popliteal artery and the popliteal vein are difficult to visualize in the adductor canal, therefore, these structures are identified by placing the probe in the popliteal crease. Below the knee, the duplicated posterior tibial and peroneal veins with their associated single arteries can be viewed with the probe at a medial location. In general, the anterior tibial veins can be ignored because they are rarely pathologic.

During this examination a number of maneuvers are necessary. First, the technologist may change from transverse to longitudinal views. When longitudinal views are used, the vein walls (proximal and distal) should be seen across the entire screen, left to right. The technologist may use the Doppler portion of the Duplex system to verify artery versus vein and determine flow direction.

With the probe, the technologist can compress the vein. The ability to fully compress the vein walls confirms vein patency and absence of thrombus formation. The technologist also looks for visible thrombus formation in the vein structures. Acute thrombi are characterized by vein dilatation and noncompressible echo lucent intraluminal material. Chronic thrombi take on a speckled ultrasonic appearance.

If the evaluated system from the common femoral vein through the tibial veins is compressible and no evidence of thrombus formation is seen, the study is considered negative for DVT. Color Doppler, Power Doppler, compression maneuvers, and respiratory maneuvers can be used to supplement this procedure, if necessary.

Superficial Venous System Assessment

Most investigators agree assessment of the superficial venous system is more challenging for the technologist and interpreting physician than the deep system.[21,22] We agree with this contention. In our facility we always perform deep system assessment in advance of superficial venous system assessment.

In contrast to the deep system, for superficial assessment we always evaluate subjects in the erect position. We have our subjects stand on a standard medical step, which is approximately 8 inches high. The patient is asked to rotate the leg of interest to expose the medial surface of the lower extremity from the groin to the ankle. To the extent possible, weight should be shifted from the leg of interest in order to relax the musculature. A degree of arm support may be needed.

With the subject properly positioned, the technician moves the probe to the inguinal ligament and produces the Mickey Mouse Image described earlier. The Mickey Mouse Image is the most important landmark of the venous examination. At his point the focus is on the Great Saphenous Vein. Starting from the three-vessel image in the transverse view the probe is moved slowly down the leg following the course of the GSV. The GSV is kept near mid-screen. The normal GSV extends from the saphenofemoral junction to the distal calf and is surrounded by superficial fascia above and muscular fascia below. As a minimum we record diameter measurements in mm and the presence of reflux (positive or negative) at three locations in the GSV (saphenofemoral junction, mid-thigh, and below knee).

Reflux is determined at locations of interest using the following technique. The technologist adjusts the color box of the Duplex system in the measurement location. The velocity scale is adjusted (maximum 25 cm/sec). While a signal is being obtained the technologist compresses the calf (below the probe) in a brisk manner. The vein highlighted in the color box should demonstrate an increase in velocity toward the heart with compression. On release the vein should demonstrate no velocity or minimal velocity away from the heart. We have found that reflux (venous flow away from the heart after release) lasting between 0.5 to 2.0 seconds is mild. Reflux is severe if present >2.0 seconds.

The same evaluation is repeated for the Small Saphenous Vein (SSV). This vein originates in the distal calf and can terminate in the upper thigh. We access this vessel with ultrasound by rotating the subject to expose the back of the legs. We identify the SSV at the distal calf, and advance over the course of the SSV. Multiple levels may be assessed; however, we generally record a characteristic SSV diameter (mm) and assess reflux in the most diseased location.

At this point it is important to note that there are variations in superficial venous anatomy. For example, the GSV may be quite small and complemented by an Anterior Accessory Saphenous Vein (AASV), which may be competent or incompetent. Further, the GSV may be duplicated in portions of its course. It is worth repeating that these variations are common and must be known and anticipated by the technologist, if a comprehensive report is to be generated.

The lower extremity has some common perforators that play significant roles in venous insufficiency. Hunterian perforating veins are located in the mid-thigh. Dodd perforating veins are located at the distal thigh. The Boyd perforating vein is located below the level of the popliteal fossa. Finally, we have Cockett #1, #2, and #3 perforating veins located, respectively, between the ankle and the lower calf. This assessment must also be part of this work-up. If present,

perforators should be assessed regarding diameter, degree of reflux, and extension to other superficial structures.

Finally, there are tributaries of the GSV and SSV that deserve attention. We look for seven tributaries in the GSV and three in the SSV. If present, we record diameter, degree of reflux, and connection to other superficial structures.

In closing, we emphasize that Duplex Ultrasound is not only diagnostic, but also plays crucial roles in endovenous ablation, ultrasound-guided sclerotherapy, and monitoring the success of vein closure procedures.

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C H A P T E R

6

Inappropriate Leukocyte Activation in Venous Disease

PHILIP COLERIDGE SMITH

INTRODUCTION

Venous ulceration remains a common problem in medical practice. A great deal has been learned about the causes of this problem, but a simple solution for all patients remains elusive. Although the presence of a leg ulcer is easy to establish, it may be the result of a number of diseases, not just venous disease. In a recent study patients with leg ulcers had venous disease, arterial disease, diabetes, lymphedema, and rheumatoid disease.[1] In this study patients had combined pathologies in 35% of cases. The overall prevalence of open venous ulceration in published epidemiological studies in adults over the age of 18 years is about 0.3%.[2–5] For every patient with an open ulcer there are probably three or four with healed venous ulcers. This means that approximately 1% of the adult population are affected by ulceration, either open or healed. Since these ulcers require regular management by health care services the cost of this disease remains high.

Venous ulceration occurs when valves fail in the deep, superficial, or perforating veins. This results in impairment of the venous muscle pumps in the lower limb.[6] Superficial venous reflux accounts for 20 to 50% of venous leg ulcers,[7,8] with deep vein and perforating vein reflux involved in many. The consequence of incompetent lower limb vein valves is that the pumping mechanism no longer reduces the pressure in the superficial veins to low levels during walking. This is reflected in the microcirculation of the skin leading, in some patients, to lipodermatosclerosis and leg ulceration.

MECHANISMS OF ULCERATION

Fibrin Cuffs

In 1982 Browse and Burnand proposed that oxygen diffusion into the tissues of the skin was restricted by a pericapillary fibrin cuff that they had observed histologically.[9] They suggested that increased capillary pressure as a consequence of venous hypertension results in an increased loss of plasma proteins through the capillary wall. This includes fibrinogen, which polymerizes to provide the fibrin cuff that may be seen around capillaries in the skin, using both histochemical and immunohistochemical methods. Subsequent measurements of fibrinolysis have shown that patients with venous disease have reduced fibrinolytic activity in the blood and veins, which might explain why the fibrin cuff persists.[10]

The clearance of ^{133}xenon from the skin as an assessment of the efficiency of the microcirculation in handling a molecule of similar size to oxygen had been measured. This gas has a molecular weight four times that of oxygen, so its diffusion rate would be half that of oxygen, assuming similar solubility for oxygen and xenon in body fluids (water). Measurements were made in the liposclerotic skin of patients with venous disease, and compared to control subjects under conditions of reactive hyperemia after five minutes of cuff occlusion of the arterial supply to the leg. No difference in xenon clearance was found between patients with venous disease and control subjects.[11] These findings lead to the conclusion that in patients with chronic venous insufficiency,

skin changes are not principally attributable to failure of skin oxygenation.

The White Cell Trapping Hypothesis

The search for alternative mechanisms of skin damage in venous disease has resulted in investigation of the blood itself. Thomas investigated a series of patients and control subjects who were subjected to experimental venous hypertension by sitting with the legs dependent for a period of 60 minutes.[12] Blood samples were taken from the great saphenous vein at the ankle. After 60 minutes patients with venous disease were trapping 30% of the white cells and control subjects were trapping 7%.

White cell margination is a normal event in the arterioles, capillaries, and venules. This phenomenon is thought to be important in the mechanism that results in tissue injury following ischemia. White blood cells are substantially larger than red cells and are responsible for many of the rheological properties of blood. White cells take 1000 times longer than red cells to deform on entering a capillary bed, and are responsible for about half the peripheral vascular resistance despite their small numbers in the circulation compared to red cells.[13] In myocardial infarction they cause capillary occlusion, which can be prevented in experimental animals by first rendering the animal leukopenic.[14,15] White blood cells have been implicated as the mediators of ischemia in many tissues including myocardium, brain, lung, and kidneys.[16–19] Polymorphonuclear leukocytes, particularly those attached to capillary endothelium, may become activated, in which cytoplasmic granules containing proteolytic enzymes are released.[20] In addition, a nonmitochondrial respiratory burst permits these cells to release free radicals, including the superoxide radical, which have nonspecific destructive effects on lipid membranes, proteins, and many connective tissue compounds.[21] Leukotactic factors also are released, attracting more polymorphonuclear cells.

In conjunction with other authors I published a hypothesis suggesting that white cell trapping resulted in neutrophil activation, causing damage to the tissues (see Figure 6.1).[22]

Based on the literature on myocardial ischemia, we proposed that white cells might cause occlusion of capillaries. If some of the capillaries were occluded this might result in heterogeneous perfusion and therefore tissue hypoxia and ischemia. This seemed a reasonable suggestion at the time, since it predated our attempts to measure the severity of the diffusion block, and we included this to explain the hypoxia observed by transcutaneous oximetry. I subsequently have concluded that this part of the original hypothesis is not of major importance in producing skin damage in patients with venous disease.

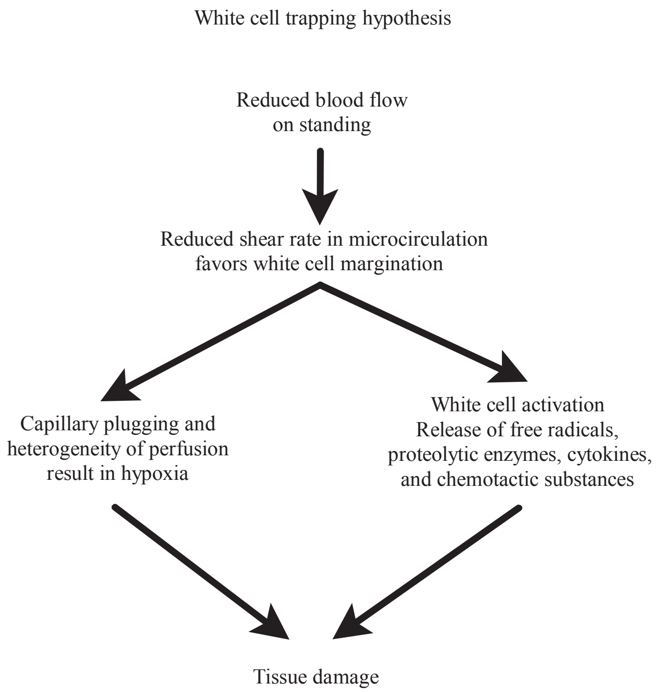

FIGURE 6.1 White cell trapping hypothesis as originally published in Reference 22.

Leukocyte Activation

The effect of venous hypertension on leukocyte activation subsequently has been studied in human volunteers using a series of plasma and cellular markers. Control subjects exposed to lower limb venous hypertension produced by standing were studied by taking blood samples from the hand and the leg veins. Degranulation of neutrophils was studied by measuring plasma levels of neutrophil elastase (a primary neutrophil granule enzyme) and lactoferrin (a secondary neutrophil granule enzyme). After a 30-minute period of experimental venous hypertension, a rise in plasma lactoferrin concentration was observed in the blood taken from both the foot and the arm.[23] When venous hypertension was produced by inflation of a cuff around one lower limb, a rise in lactoferrin was observed only in that limb. Subsequently expression of the surface neutrophil ligand, CD11b, has been investigated as a marker of neutrophil activation. The experiment was repeated as before on control subjects. Blood was taken from a dorsal foot vein. CD11b expression was assessed by fluorescent labelled monoclonal antibody used to label neutrophils in whole blood, which were counted using flow cytometry. During the period of venous hypertension in control subjects no rise in CD11b expression was seen in the lower limb blood.[24] Following return to the supine position, when neutrophils might be expected to leave the lower limb, according to the studies of Thomas,[12] increased levels of CD11b were observed. This indicates

that neutrophils were upregulated by their period of adhesion to normal endothelium. An increased white cell : red cell ratio also was observed during this phase, confirming white cell egress from the lower limb.

A similar study also has been conducted in patients with venous disease, including only subjects with unulcerated skin to avoid the possibility that the inflammatory processes involved in the ulcer may result in up-regulation of inflammatory mediators in a way unrelated to the development of the ulcer. Two groups of patients were studied: one group with uncomplicated varicose veins and one with skin changes (lipodermatosclerosis) attributable to venous disease. The adhesion of neutrophils and monocytes to endothelium was investigated. This is a two-stage process. Initially these cells roll along the endothelium, binding in a loose manner using a ligand on the leukocytes known as CD62L or L-selectin. When binding occurs a fragment of L-selectin is released into the plasma (soluble L-selectin) and can be detected by an ELISA. It was found that the concentration of soluble L-selectin rose during venous hypertension, confirming that endothelial : leukocyte binding had occurred. There was no major difference in magnitude between the two groups of patients.[25]

Subsequently, firm binding of neutrophils and monocytes occurs using CD11b/CD18 ligands, which link to endothelial ICAM. This is reflected in the peripheral blood by a fall in the cells expressing most CD11b. Just such a fall was seen in the blood taken from the leg in both groups of patients. On return to the supine position I had expected to see an egress of leukocytes expressing more CD11b in these patients, but this was not observed, in contrast to the studies on control subjects. In the time-scale of this experiment (up to 10 minutes following venous hypertension), the more activated neutrophils and monocytes remained bound to the endothelium of the lower limb.[26]

Plasma lactoferrin and elastase have been assessed in groups of patients with active venous disease. Blood was taken from the arm veins (not the lower limb veins) of patients with varicose veins, liposclerotic skin change, and active venous ulceration.[27,28] In all samples, the levels of lactoferrin and elastase were higher in the patients than the age and sex-matched control groups (see Figures 6.2 and 6.3).

However, it was found that the highest levels of plasma lactoferrin were present in patients with active varicose veins. Subsequently blood was taken from the arms of patients for measurement of neutrophil CD11b expression. This was elevated in patients with varicose veins, but depressed in patients with lipodermatosclerosis.[29] The explanation may be that the more active leukocytes are attracted to the region of the inflammatory process and do not circulate in the peripheral blood. Alternatively, such patients may have high circulating levels of neutrophil inhibitors.

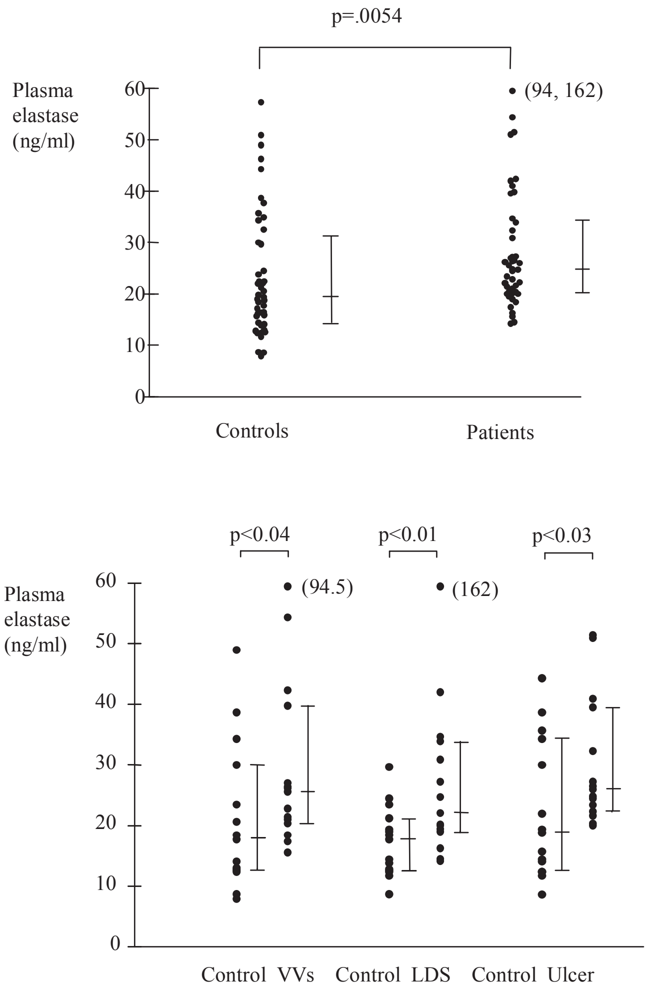

FIGURE 6.2 Results of plasma neutrophil elastase measurements in patients and control subjects. Error bars show the median and interquartile range of data. Statistical significance was tested by the Mann-Whitney U test.

Histology

Histological studies have been used to investigate the biological processes at work in the skin in chronic venous disease. A quantitative histological study has been reported in which three groups of patients were studied.[30] The first was a group of patients with no evidence of skin changes as a consequence of their venous disease. The next group exhibited lipodermatosclerosis without a history of ulceration. The third group had healed ulcers with residual lipodermatosclerosis. Patients with normal skin had a low number of white blood cells visible (4 per mm^2) in the upper 0.5 mm of the skin. There were eight times as many in patients with liposclerotic skin, and 40 times as many in patients with healed venous ulcers. Subsequently an immunohistological study was undertaken to determine the types of white cell present in this infiltrate.[31] The majority of cells

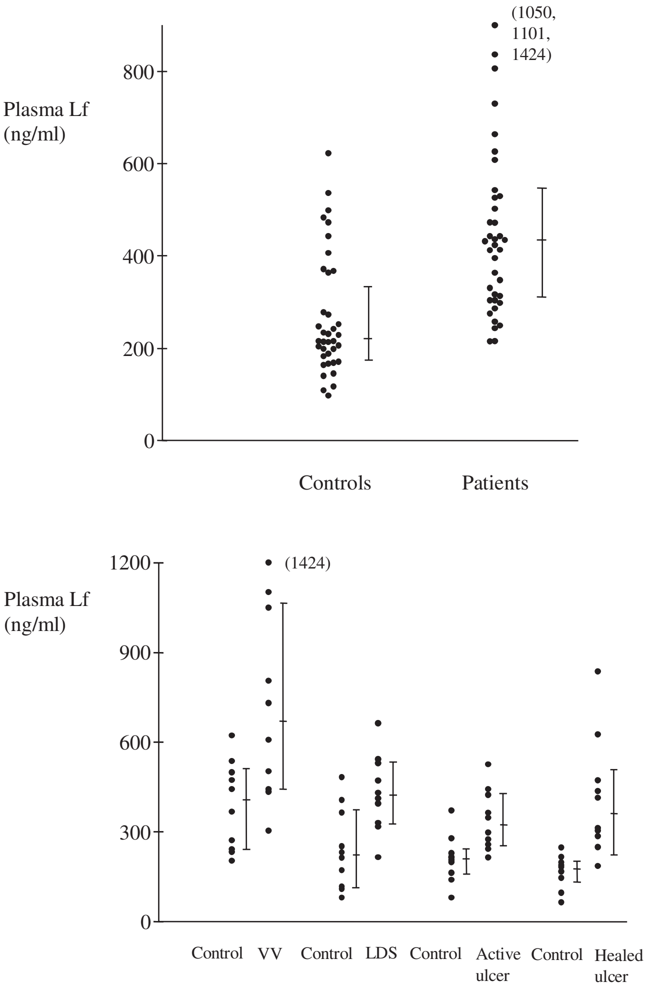

FIGURE 6.3 Results of plasma neutrophil lactoferrin measurements in patients and control subjects. Error bars show the median and interquartile range of data.

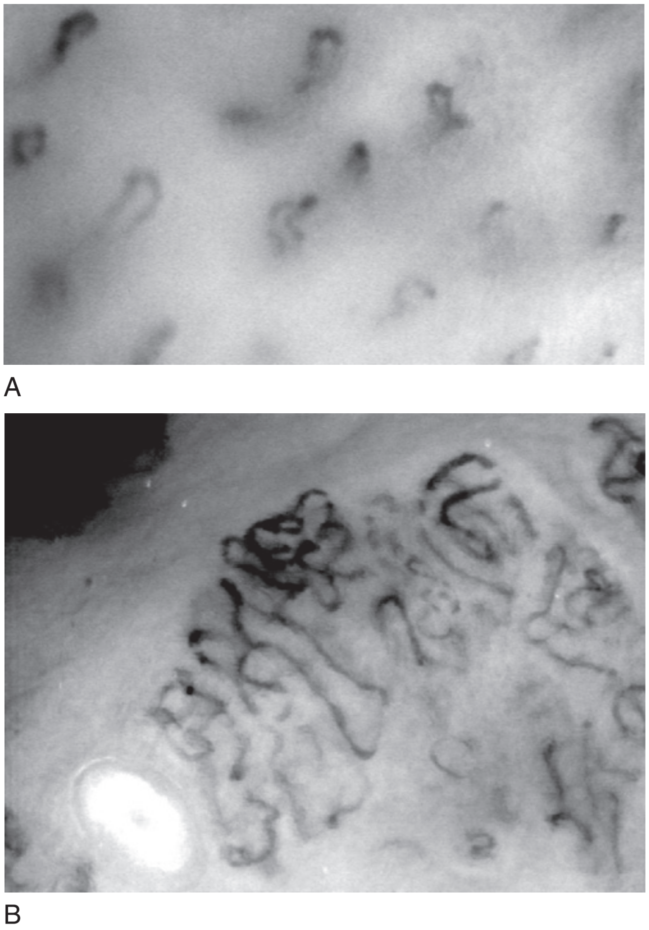

FIGURE 6.4 Images from the capillary microscope. Normal capillary loops in the skin of the lower limb show one reversal of direction as the vessel rises to the top of the papillary dermis and then descends (a). In a patient with lipodermatosclerosis, numerous convolutions are seen in each capillary (b).

are macrophages with a T-lymphocyte component, but no excess of neutrophils compared with control sections taken from normal limbs. So this infiltrate is a reflection of a chronic inflammatory process.

The Endothelium

The microcirculation of the skin has been investigated by histology[32] and by capillary microscopy.[33] Both methods demonstrate capillary proliferation in patients with CVI—vastly more capillaries are visible by both techniques (see Figure 6.4). However, capillary microscopy shows that these probably arise from a single capillary loop and appear like a glomerulus, rather than an increase in the numbers of capillaries. Quantitative measurement of the capillary convolution in patients from each of the CEAP clinical classes has been published (see Figure 6.5).[34] Immunohistochemical investigations have shown that the pericapillary cuff contains far more than fibrin. The capillary endothelium is perturbed, expressing increased amounts of factor VIII–related antigen[31,35] and adhesion molecules, especially ICAM-1. ELAM-1 may be slightly upregulated but VCAM appears to be normal in patients without venous ulceration. Perturbed endothelium is more likely to attract the adhesion of leukocytes. The presence of the peri-capillary fibrin cuff has been confirmed, but it also contains collagen IV, laminin, fibronectin, and tenascin.[36] A strong leukocyte infiltration has been measured in patients with venous disease.[37] These cells are macrophages and T-lymphocytes. The cytokines involved include IL-1α and IL-1β. TNFα has not been detected in these histological sections. The presence of the perivascular fibrin cuff (with other components) is a reflection of the inflammatory process and is seen in other chronic inflammatory conditions. In patients with venous disease, increased plasma D-dimer levels have been observed, sug-

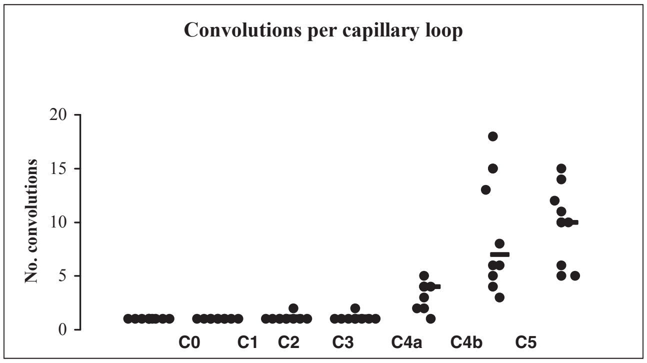

FIGURE 6.5 This graph shows the results of analysis of the number of convolutions per capillary loop in images such as those shown in Figure 6.4. The vertical axis shows the number of convolutions per capillary in CEAP stages C0–C5. Capillary abnormalities are mainly present in C4a, C4b, and C5 limbs.

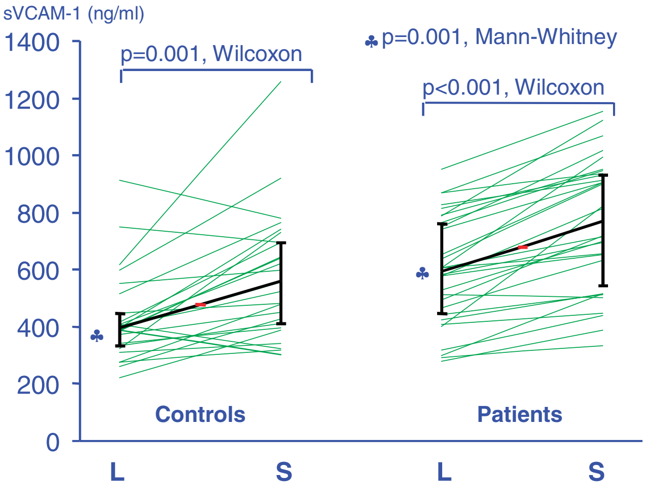

FIGURE 6.6 Plasma VCAM-1 levels in normal controls and patients with chronic venous disease (with and without skin changes), before and after venous hypertension produced by sitting with the lower limbs dependent for 30 mins. Descriptors: medians and inter-quartile ranges; statistics; Wilcoxon and Mann-Whitney U tests for unpaired data. L = lying, S = standing.

gesting enhanced deposition of fibrin.[38] The perturbed state of the endothelium allows the passage of large molecules though the endothelium permitting their perivascular accumulation, and explains the presence of the fibrin cuff.

A search for systemic markers of endothelial activation has been performed by undertaking measurements of plasma levels of soluble endothelial adhesion molecules and von Willebrand factor.[39] Patients with chronic venous disease (a group with uncomplicated varicose veins and a group with skin changes) again were studied and compared to normal controls. The concentration of soluble VCAM (vascular endothelial adhesion molecule) was elevated in both patient groups compared to control subjects, and was highest in the group with skin changes (see Figure 6.6).

Histological Search for Angiogenic Factors

The vascular proliferation seen in the skin of patients with venous disease has been known for many years, but has not been explained. In recent years many angiogenic factors that stimulate the growth of blood vessels have been recognized. Immunohistochemistry was used to evaluate the presence of a number of such factors in the skin of patients with venous disease.[40] Skin biopsies were taken at the time of surgery for varicose veins from the legs of patients with and without skin changes as well as of breast skin in patients without clinical evidence of venous disease, for use as a control. There was an increase in platelet derived growth factor, subtype BB (PDGF-BB) in patients with venous disease. This was found in the capillary wall in vessels of the dermal papillae. There was also considerable upregulation of the production of vascular endothelial growth factor (VEGF) in the epidermis of patients with venous disease, most marked in those with skin changes. It seems likely that VEGF may account for at least some of the vascular proliferation seen in the skin of patients with venous disease. This growth factor is also responsible for increased vascular permeability to large molecules, a feature of the skin microangiopathy that has been reported from capillary microscopy studies.[33] The mechanism of stimulation of epidermal VEGF production is unclear at present.

Skin Fibrosis in Venous Disease

The role of TGF–β_1 in the skin damage of CVI has been studied in considerable detail by Pappas et al. using immunohistochemical examination, electron microscopy, and examination of TGF–β_1 gene expression.[41] This investigation indicated that activated leukocytes traverse perivascular cuffs and release active TGF–β_1. Positive TGF–β_1 staining of dermal fibroblasts was observed and suggests that fibroblasts are the targets of activated interstitial leukocytes. A potential mechanism for quick access and release is storage of TGF–β_1 in the extracellular matrix. TGF–β_1 was elevated exclusively in areas of clinically active disease, indicating a localized response to injury. These data suggest that alterations in tissue remodelling occurs in patients with CVI and that dermal tissue fibrosis in CVI is regulated by TGF–β_1.

The fibrosis seen in the skin of patients with lipodermatosclerosis also has been investigated by other authors.[42] This study shows that enhanced cell proliferation and an increase in the number of procollagen mRNA-expressing fibroblasts contribute to the development of LDS (see Figure 6.7). The fibrotic changes that result may not only be

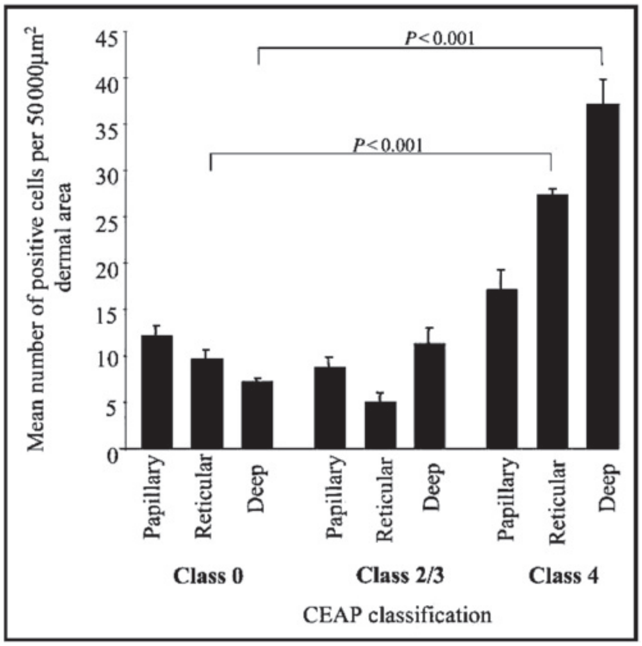

FIGURE 6.7 From Reference 42. Increased procollagen type I-expressing cells in lipodermatosclerotic (LDS) skin. The number of positive dermal cells, as demonstrated by in-situ hybridization, was assessed in skin sections from the control patients (CEAP class 0, n = 12), from patients with chronic venous insufficiency but no clinical evidence of LDS (CEAP class 2⁄3, n = 10), and from patients with LDS (CEAP class 4, n = 12). Data represent mean and SEM.

mediated by inflammatory cell-derived factors but by additional profibrotic agents released in the skin as a consequence of chronic venous hypertension.

Some authors have studied the distribution of growth substances and connective tissue proteins in skin biopsies using immunohistochemical staining.[43] In particular they studied the pericapillary cuffs, which were once thought to inhibit oxygen transfer to the tissues. The cuffs were positive for actin, type IV collagen, factor XIIIa, and alpha 2-macroglobulin, and there was increased TGF–β_1. They observed that TGF–β_1 immunoreactivity was present within the fibrin cuffs, but not in the provisional matrix in the ulcer bed around the cuffs. These observations suggest that growth factors critical in wound healing, such as TGF–β_1, are present within venous ulcers, but are abnormally distributed. Their distribution within fibrin cuffs and colocalization with extravasated plasma proteins, particularly alpha 2-macroglobulin, which is a recognized scavenger molecule for TGFβ and other growth factors, provides evidence for a possible trapping of growth factors in venous ulcers. This proposal has been advanced as a cause for failure of venous leg ulcers to heal.[44]

Interpretation of Data from Existing Studies

Endothelial adhesion is a normal physiological activity of neutrophils and monocytes. During venous hypertension the fall in blood flow to the lower limb and increase in diameter of capillaries result in a fall in the shear rate in cutaneous capillaries. This favors leukocyte adhesion, which may be observed, even in control subjects, but is of greater magnitude in patients with venous disease, presumably due to the modifications that take place in the endothelium in chronic venous disease.

It has been found that leukocyte-endothelial interaction occurs during short-term venous hypertension (within 30 minutes) and that during this period neutrophil degranulation may be detected, releasing primary and secondary granule enzymes into the region of the endothelium. At the same time an increase in von Willebrand factor and soluble endothelial adhesion molecules can be found in the leg blood. These arguments apply to control subjects as well as to patients, although the magnitude of change is always greater in the patients rather than the control subjects. The research shows that when the venous system becomes deranged, endothelial injury may be the result. Activated leukocytes leave the lower limbs of control subjects following venous hypertension. In patients with venous disease, these cells appear to remain in the lower limb, perhaps attached to the abnormal endothelium.

The chronic changes seen in liposclerotic skin may be the response to sustained, low-grade injury to the endothelium by neutrophils and monocytes over many months or years. The perivascular infiltration of vessels in the papillary dermis by macrophages and T-lymphocytes may simply be a tissue response to the chronic inflammatory processes referred to earlier (see Figure 6.8). Endothelial activation is seen during this phase with increased expression of endothelial adhesion molecules. This would favor the adhesion of further leukocytes encouraging this process to continue.

The chronic inflammatory process results in the release of cytokines, which encourage vascular proliferation. VEGF has been shown to be involved in this process. Whether this is simply an associated phenomenon or crucial to subsequent ulceration remains unclear at present. Extensive skin fibrosis, which is part of the clinical syndrome of lipodermatosclerosis, is a feature of chronic venous disease. The macrophages present in the perivascular inflammatory process release TGFβ, and this in turn stimulates fibroblasts to synthesize more collagen and connective tissue proteins.

The progression from the chronic skin damage to actual ulceration remains difficult to understand. A possible explanation is that an initiating stimulus causes massive activation of the peri-vascular macrophages, resulting in extensive tissue and blood vessel destruction. This might occur spontaneously or minor trauma to the region may set in motion the series of events that lead to ulcer formation.

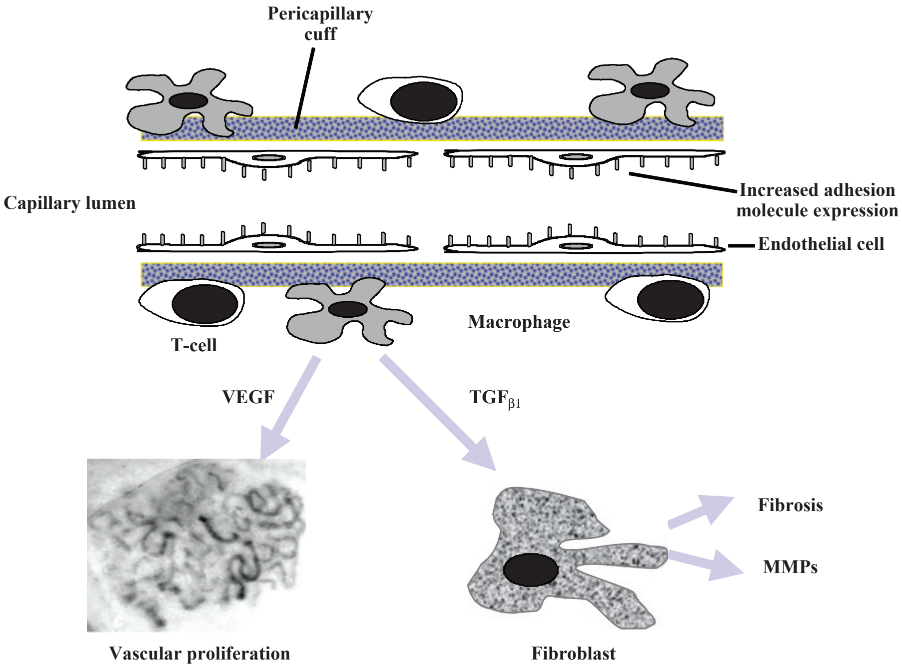

FIGURE 6.8 Diagrammatic summary of findings from many investigations in skin capillaries in patients with chronic venous disease. The capillaries comprise endothelial cells showing activation. The vessels are surrounded by an inflammatory cuff with a cellular infiltrate, which includes macrophages. These and other cell types release a range of cytokines that, among other things, produce vascular proliferation and skin fibrosis.

The data collected in the studies of neutrophil, monocyte, and endothelial cell activity have so far failed to identify major differences between those patients who develop skin changes and are at risk of ulceration and those who do not. Inflammatory mechanisms are very complex and identifying those which predispose to the development of skin changes and ulceration will be a complex task.

Implications for Pharmacological Treatment in Venous Disease

Although bandaging and stockings have been used effectively in the treatment of chronic venous insufficiency for many years, modern pharmacological science may provide assistance in healing venous ulcers and perhaps some insight into the mechanisms of the disease.

Pentoxifylline has been used for the treatment of claudication for a number of years, with moderate success. Its mechanism of action is probably through an effect on inhibition of cytokine-mediated neutrophil activation.[45] Its efficacy in healing venous leg ulcers has been reported in a recent meta-analysis.[46] Nine trials involving 572 adults were included. Pentoxifylline plus compression is more effective than placebo plus compression (relative risk of healing with pentoxifylline 1.30, 95% confidence interval 1.10–1.54). This drug could be considered for use in patients with venous leg ulceration when used in combination with compression.

Prostaglandin E_1 (PGE_1) has a number of profound effects on the microcirculation, including reduction of white cell activation, platelet aggregation inhibition, small vessel vasodilatation, and reduction of vessel wall cholesterol levels. Recently the results of a randomized, placebo-controlled, single blind study in which 87 patients who had venous leg ulcers has been reported.[47] Patients were treated with compression bandaging and conventional wound management. They also received treatment for 20 days with an infusion of prostaglandin E_1 analogue (Prostavasin, Schwarz Pharma) or placebo. After four months, all ulcers were healed in the active treatment group but only 32 of 38 in the placebo group. This is a potentially useful drug but the limitation of giving intravenous infusions restricts it applicability.

Laurent et al. investigated micronized purified flavonoid fraction (MPFF)[48] and showed that this drug reduced the symptoms of venous disease (aching, itching, feeling of swelling) and also reduced ankle edema. More recently MPFF has been studied for its effects on venous leg ulcer healing. A meta-analysis has been published in which five prospective, randomized, controlled studies involving 723 patients with venous ulcers were included.[49] Patients were treated with compression bandaging and local wound care in all cases. In two studies MPFF was compared to placebo

and in three studies MPFF was compared to standard treatment alone. At six months, the chance of healing ulcer was 32% better in patients treated with adjunctive MPFF than in those managed by conventional therapy alone. The main benefit of MPFF was present in the subgroup of ulcers between 5 and 10 cm^2 in area and those present for six to 12 months duration. MPFF therefore may be a useful drug to combine with compression management in countries where it is licensed.

CONCLUSIONS

The precise mechanisms through which venous hypertension causes ulceration remain to be discovered. There is clear evidence of leukocyte activation in venous disease and many inflammatory mechanisms are upregulated in the skin. So far it has been impossible to say which of these is the main cause of the problem and which are simply a response to the inflammatory process. Drugs that mitigate leukocyte activation appear to benefit ulcer healing. A better understanding of the initiating processes may lead to improvements in the management of patients with venous ulceration.

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C H A P T E R

7

Molecular Basis of Venous Insufficiency

GEERT W. SCHMID-SCHÖNBEIN

INTRODUCTION

Chronic venous disease (CVD) of the lower limb reaches its most severe form as varicose veins and venous leg ulcers. But before reaching such endstages, CVD goes through a range of manifestations that also include edema and skin changes (venous eczema, ankle skin hyperpigmentation, atrophie blanche, and lipodermatosclerosis). Robust evidence has now been gathered to indicate that CVI is an inflammatory disease. This recognition has facilitated understanding the pathophysiological processes that underlie these diverse manifestations, particularly at the cellular and molecular levels. The recognition that an inflammatory process may be involved has opened a range of opportunities for development of novel interventions. But it also has opened the door to an analysis that may lead us toward the trigger mechanisms for inflammation in CVD; That is, an understanding of the origin of the earliest manifestations (like telangiectasia) and the key to future design of preventions.

TISSUE RESTRUCTURING

The inflammatory process and lesions in different stages of CVD involve the superficial layers of the skin but possibly also various venous valves, some of which may be located deep. Capillary density may vary in liposclerotic skin. For example, some areas of white atrophy (atrophie blanche) may show a complete loss of capillaries in some areas whereas in others, the capillaries appear dilated, elongated, coiled, and tortuous.[1] Endothelial lesions in the capillaries have been observed. These include irregular wavy shapes of the luminal surface, intracellular edema, and increased intra-cytoplasmic vesicles. Basement membranes appear to be completely fused with the surrounding tissue. Pericapillary spaces are filled with a fluid that is rich in cellular fragments and proteins. Pericytes and fibrin cuffs have been observed in the pericapillary spaces and around the capillaries.[2] In capillaries per se there is red cell packing, white blood cells, and platelet aggregates that may fill the capillary lumen and may be found in the pericapillary tissue.

In addition there is failure of valves through dilation of the venous wall and remodeling of the valve leaflets dilation of the valvular annulus, bulging and stretching of valve leaflets, commissural dilation, shortening, tearing and perforation of leaflets, and, finally, complete destruction of the valve.[3,4] Furthermore, ultrastructural and immunohistochemical studies of valves and the venous wall have revealed leukocytes adhering and transmigrating into the venous wall.[5,6]

EARLY MANIFESTATIONS OF INFLAMMATION

The suggestion that inflammation may be involved in CVD comes from the evidence for elevated endothelial permeability,[2] a process that tends to involve inter-endothelial junctions. This can readily be observed in acute models of venous hypertension (see Figure 7.1). Although there are a large number of mediators (histamine, platelet activating factor, cytokines) that have the ability to elevate endothelial permeability, most of them when acutely applied to a tissue act transiently via mechanisms that involve nitric oxide,[7] actin polymerization, and selected small GTPases.[8–15] This serves as an indication that already an early event in CVD

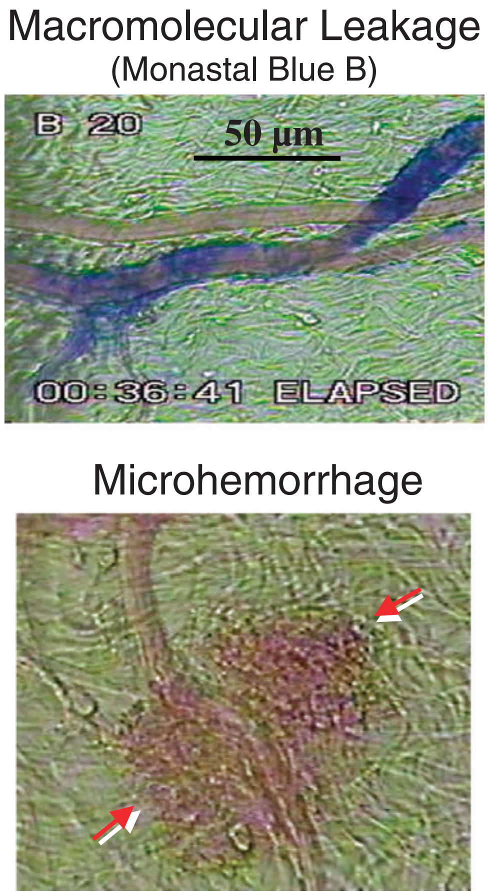

FIGURE 7.1 Short-term venous pressure elevations cause elevated microvascular permeability and red cell diathesis. Intravital micrographs showing evidence for elevation of venular permeability (detected by monastral blue escape across the endothelium, top panel) and extravasation of red cells across postcapillary venules in rat mesentery (bottom panel) after occlusion of a larger downstream venule (about 500 μm) for 1 hour followed by 1 hour reperfusion. Adapted from (63).

is possibly driven by mechanisms that have the ability to produce a chronic inflammatory state. The reduction of endothelial permeability may be a target of opportunity for early intervention since it may interrupt the inflammatory cascade at one of its earlier steps. Elevation of endothelial permeability with opening of leakage sites between endothelial cells depends on the inter-endothelial adhesion molecule VE-cadherin,[16] an enzyme sensitive glycocalyx layer on the endothelial cells,[17] on the specific venular genotypes,[18] and on exercise training.[19]

TISSUE REMODELING AND ENZYMATIC ACTIVITY

The link between inflammation and skin changes may be by way of the proteolytic enzymes, including Ca/Zn-dependent endoproteinases (matrix metalloproteinases, MMPs) and serine proteinases. Chronic dermal ulcers are characterized by excessive proteolytic activity, which degrades extracellular matrix and growth factors and their receptors. The MMP family of proteases (all of them can be inhibited by metal chelation) are positioned on extracellular matrix proteins in an inactive proform. They play an important role in cell differentiation and development.[20] MMPs may be released from preexisting pools (cytoplasmic granules) upon stimulation and endocytosis or may be newly synthesized by several types of cardiovascular cells.[21] The inactive pro-enzymes can be activated by other proteinases, including those produced by mast cells.[22] MMPs have multiple binding sites but cleave collagen at unique sites.[23] The MMP levels in wound fluids from chronic wounds tend to be significantly higher than from acute wounds and healing is associated with reduced MMP activity.[24]

The expression levels of MMPs can be controlled by mechanical stretch (strain) (see Figure 7.2), but in a way that depends on the time course of the strain. This has been studied on smooth muscle cells in an in-vitro chamber subject to oscillatory and constant strain. Stationary strain significantly increases MMP-2 mRNA levels at all time points, whereas cyclic strain decreases it after 48 h. Both secreted and cell-associated pro-MMP-2 levels are increased by stationary strain at all times, whereas cyclic strain decreases secreted levels after 48 hours. MMP-9 mRNA levels and pro-MMP-9 protein are increased after 48 hours of stationary strain compared with both no strain and cyclic strain.[25]

Neutrophils, besides a rich protease population in their primary and secondary granules, also have several MMPs. There is gelatinolytic activity discharged by MMP-9, MMP-8 a neutrophil collagenase, leukolysin a membrane-type MMP.[26] Evidence from knock-out experiments suggests that MMP-9 acts upstream of neutrophil elastase by proteolytically inactivating neutrophil elastase inhibitor a1-PI[27] and that it can activate other MMPs.[28] Extracellular MMP inducer (EMMPRIN; CD147) has been observed to increase MMP expression, and membrane type 1 MMP (MT1-MMP) has been implicated in the activation of MMPs. Venous leg ulcers have elevated expression of EMMPRIN, MMP-2, MT1-MMP, and MT2-MMP.[29]

Clearly, these proteases will remain of major interest because of their involvement in both the inflammatory reaction and the remodeling of cutaneous tissue.[30] Current interest is focused on MMP1, MMP2, MMP9, MMP12, MMP13, TIMP1, and TIMP2.[31–33] The overexpression of MMP-3 (stromelysin-1) and MMP-13 (collagenase-3) is associated with nonhealing wounds.[34] Recent studies showed an increased expression of MMP2 and TIMP1 in lipodermatosclerotic skin,[30,35] in venous leg ulcers,[29] and in wound fluid from nonhealing venous ulcers.[37] Expression of MMP9 has been observed to be upregulated on the edges of intractable venous ulcers[35] and the rate of MMP-9 activation in plasma

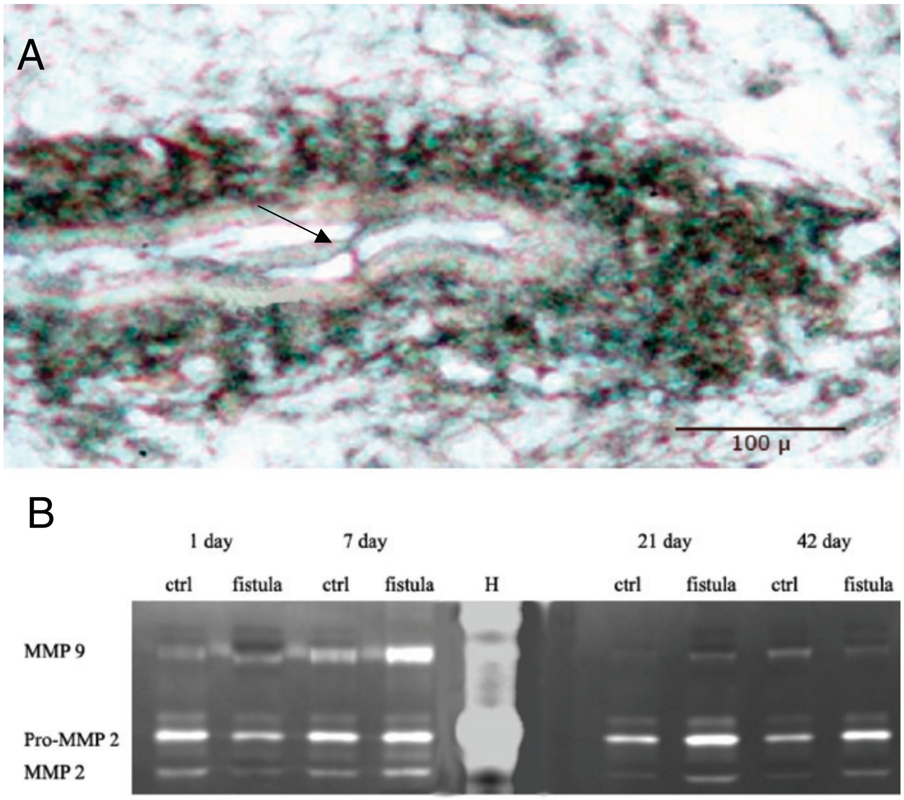

FIGURE 7.2 MMP activation in the early phases of venous hypertension. (A) Immunohistochemical labeling of paraffin section of rat femoral vein after placement of an arteriolar/venular fistula for one week to raise venous pressure. The vein still has an intact valve but the distension leads to extensive expression of MMP2 (detected by deposition of biotin avidin enzymatic reaction product (dark brown color) in the media of the vein. (B) Gel electrophoresis zymography of saphenous vein segments subjected to the hypertension by placement of an arterial/venous fistula. The four left lanes are from 1 day and 7 day; each experimental group is paired with the control represented by the contralateral vein; the center "H" lane represents human MMP-2 and MMP-9 standards; the four right lanes are from the later time points at 21 and 42 days; each experimental group is paired with the control represented by the contralateral vein. Vein segments subjected to the fistula present significantly higher level of MMP-9 at 7 days from the creation of the fistula. Higher levels of pro-MMP2 and MMP-2 were observed at 21 and 42 days from the creation of the fistula. Adapted from (148).

of patients with severe CVD is elevated.[36] Levels of TIMP-2 are lower in lipodermatosclerotic skin and ulcers.[30,37] Unrestrained MMP activity may contribute to extracellular matrix protein breakdown that impairs healing. Proteolytic reactions may be even of greater importance than other cytotoxic reactions, such as oxygen free radical production.

The skin hyperpigmentation seen in lipodermatosclerosis may not just be an innocent byproduct of capillary hyperpermeability. The extravasation of red blood cells leads to oxidative stress[38] as well as elevated ferritin and ferric iron levels in affected skin that causes hydroxyl radical formation,[39–41] possible MMP activation, and development of a local microenvironment that exacerbates tissue damage and delays healing.[42] Consistent with this, the hemochromatosis C282Y mutation (a common genetic defect of iron metabolism) is associated with a near 7-fold increase in risk of ulceration among CVD patients.[43]

A critical issue are not only the mechanisms that cause expression of these proteases, but also the mechanisms that cause their activation and the often lack of anti-protease activity. Among the mechanisms that have been proposed to activate MMPs is plasmin,[44] serine proteaseses like trypsin,[45] MMP-3, and MMP-13.[33] These may involve indirect pathways, indicating the possible complexity of the activation process involved. Plasmin stimulates pro-MMP enzyme conversion to the active form. Plasmin hyperactivity due to decreased plasminogen activator inhibitor-1 (PAI-1) may thus cause MMP overactivity.[44] But these are important regulatory pathways that need to be clarified to understand the activation of the proteolytic process that causes restructuring in venous disease (see later).

LEUKOCYTE ENTRAPMENT AND MOLECULAR ADHESION MECHANISMS

The modern developments of the pathophysiological basis of the skin changes in CVD can perhaps be traced back to the simple observation that leukocytes have quite different biomechanical properties than the red cells. Even though they are clearly in the minority, they contribute to many microvascular events.[46,47] One of them is local accumulation in the microcirculation and thus it is highly significant that blood returning from feet that have been passively dependent for 40 to 60 minutes is relatively depleted of leukocytes, especially in patients with CVD.[48–50] Leukocytes are easily trapped in the microcirculation due to their stiff cytoplasmic properties and their ability to express membrane adhesion molecules, further enhanced by the fact that these properties are changed dramatically after activation.[51] This subtle mechanism suggests that leukocytes accumulate in the lower extremity under conditions of high venous pressure. It is possible that the accumulation in microvessels is due to the fact that the cells are already activated in the central circulation,[6,52] which means that they may be stimulated in the circulation by a mechanism that could be located outside of the venous network of the lower extremities. Alternatively leukocytes become entrapped in the skin microcirculation by adhesion to the endothelium, which is activated by a local process not necessarily dependent on the same mechanisms that causes leukocyte activation. The leukocyte adhesion is to the membrane of the endothelium of small vessels, especially capillaries and post-capillary venules. The accumulated leukocytes became activated and led to the suggestion that an inflammatory reaction is important in provoking skin changes in CVD. Numerous recent studies have added weight to that suggestion.[53–55] Most interesting in this respect are the observations by Coleridge-Smith and his colleagues, showing degranulation of the leukocytes with an increase of neutrophil elastase and lactoferrin, markers of neutrophil activation, in patients under transient conditions of venous hypertension and with chronic venous insufficiency.[56–58] These enzymes may be effective activators of other proenzymes, such as MMPs. The circulating mononuclear cells of patients with CVD also have reduced degree of proliferation in response to a mitogenic challenge (staphylococcal enterotoxins) and thus a reduced capacity for wound healing.[59]

Skin biopsies from CVD limbs show elevated numbers of macrophages, T-lymphocytes, and mast cells.[60,61] This is the same pattern as observed in both acute[62,63] and chronic[64] experimental rat models of venous hypertension, with elevated levels of tissue leukocytes in skin samples from affected limbs, but not from sham-operated controls.

The molecular mechanisms involved in leukocyte adhesion and activation in CVD patients are now beginning to be elucidated. For example, transient binding of L-selectin on the leucocyte surface to E-selectin on endothelial cells is involved in leukocyte "rolling" along the endothelial surface. However, when leukocytes are activated they shed L-selectin into the plasma and express molecules of the integrin family, including CD11b that binds to intercellular adhesion molecule-1 (ICAM-1). Integrin binding promotes firm adhesion of leukocytes, the starting point for their migration out of the vasculature and degranulation.

The evidence in CVD suggests that a variety of membrane adhesion molecules on endothelial cells and leukocytes (ICAM-1, vascular cell adhesion molecule-1, LFA-1, VLA-4, Mac 1, and others) appear to facilitate the adhesion and stimulate projection of pseudopodia as a requirement for transmigration of the leukocyte into the venous wall.[65–68] The leukocyte infiltration of the venous parenchyma is accompanied by remodeling of the extracellular matrix, a process that is ultimately responsible for the destruction of the venous valves.

At the same time, plasma levels of soluble L-selectin increase, reflecting the shedding of these molecules from leukocyte membranes during leukocyte-endothelial adhesion.[69] Similarly, basal plasma levels of the adhesion molecules ICAM-1, endothelial leukocyte adhesion molecule-1 (ELAM-1), and vascular cell adhesion molecule-1 (VCAM-1) are higher in CVD patients than controls and increased significantly in response to venous hypertension provoked by standing.[67]

In addition to local factors operating in relation to venous hypertension, CVD patients have a tendency for systemically elevated leukocyte adhesion. Plasma obtained from CVD patients induced higher degrees of activation (assessed by oxygen-free radical production and pseudopod formation) in healthy, naive granulocytes than did plasma taken from normal subjects.[6] The nature of the plasma factor responsible is presently unknown.

CYTOKINES

Even though it is well recognized that cytokines are part of the inflammatory reaction in CVD[65,70,71] no clear picture exists about their exact role. For example treatment with granulocyte/monocyte colony stimulating factor (GM-CSF) leads to mixed results in ulcer healing. TNFα, whose expression is enhanced in many inflammatory reactions, stimulates the expression of inflammatory adhesion molecules, the synthesis and release of other cytokines, and the chemotaxis of neutrophils and macrophages. The expression of TNFα appears to be upregulated in patients

with venous ulcers and healing of the ulcer may reduce the level of TNFα.[72]

GROWTH FACTORS

In lipodermatosclerosis, the skin capillaries become elongated and tortuous,[73] and may take on a glomerular appearance in more advanced skin changes,[74] with proliferation of the capillary endothelium. Vascular endothelial growth factor (VEGF) is an obvious candidate for involvement in these changes, and has been shown to increase microvascular permeability.[75] Plasma levels of VEGF increase during the venous hypertension-induced short-term standing in both normal subjects and CVD patients, but are higher in patients than in normal controls.[76] Furthermore, plasma VEGF levels are higher in CVD patients with skin changes than in CVD patients with normal skin.[77] VEGF also is known to induce the expression of adhesion molecules, such as ICAM-1, VCAM-1, and E-Selectin.[78] Both VEGF expression and its receptor expression (Flk-1/KDR) are upregulated under variations of blood shear stress and with the inflammatory reaction.[79,80] The level of VEGF increases with the severity of the disease and the CEAP score.

Another feature of the skin changes associated with CVD is dermal tissue fibrosis. Transforming growth factor-β_1 (TGF-β_1) is a known fibrogenic cytokine. Immunocytochemical analysis of punch biopsy specimens showed that skin from the lower calf of CVD patients had significantly elevated active TGF-β_1 levels compared with normal skin or skin taken from the thigh region of the same patients.[61,81] The TGF-β_1 was located in leukocytes, fibroblasts, and on collagen fibrils, and Pappas proposed that activated leukocytes migrate out of the vasculature and release TGF-β_1, stimulating increased collagen production by dermal fibroblasts and leading to dermal fibrosis.[81]

It is evident that analysis of the inflammatory cascade in venous disease has just begun. Many details will be revealed in the future especially at the molecular level, which will open new opportunities for intervention. But I like to draw attention to another issue important in the contact of inflammation. The inflammatory cascade serves under normal conditions as a repair mechanism after tissue injury. One should ask then, why are there skin lesions, which for long periods of time do not proceed to a resolution of the inflammation? There may be mechanisms that serve to maintain an inflammatory state, but it is possible that the trigger mechanism that set into motion the first step in the inflammatory cascade is never quite eliminated in chronic conditions. Thus, we need to engage in an analysis of possible trigger mechanisms for inflammation in CVD.

TRIGGER MECHANISMS FOR CELL ACTIVATION

There are a large number of primary mechanisms that may serve to activate cells and stimulate an inflammatory cascade in the circulation. It is helpful to classify these mechanisms into several general categories:

a) Positive feedback mechanisms: There exists a class of inflammatory reactions that are mediated by direct action of plasma inflammatory stimulators (oxygen free radicals,[82] platelet activating factor (PAF),[83] cytokines (e.g., TNF-α, IL-1, IL-8),[84] complement fragments,[85] endotoxins, coagulation and fibrinolytic factors, leukotrienes, thrombin, and oxidized LDL). The list of inflammatory mediators is long, and may in part be triggered by trauma or by bacterial, viral, or fungal sources.
b) Negative feedback mechanisms: An alternative pathway for cell upregulation in the microcirculation is by depletion of anti-inflammatory factors. This list is somewhat shorter and includes nitric oxide, adenosine, glucocorticoids, selected cytokines (e.g., IL-10),[86] estrogen,[87] and some proteins like albumin.
c) Contact activation: A specialized form of cell activation by membrane contact has been proposed in the form of juxtacrine activation.[88] A nonactivated endothelial cell may be stimulated during membrane contact by an activated leukocyte and vice versa, for example, by oxygen free radical production in the membrane contact region between the cells and by formation of platelet activating factor (PAF) and other bioactive lipids.
d) Activation by mechanotransduction: These mechanisms for cell activation involve fluid shear stress (force per unit area parallel to a surface) and normal stress (for per unit area normal to a surface, i.e., pressure). These two mechanical stresses likely play an important role in venous disease (see later).
e) Activation by physical transients: Transients of gas concentrations (like oxygen, carbon dioxide, etc.) or also temperature transients have the ability to stimulate cell activation irrespective of the direction of the transient (up or down) but dependent on the magnitude of the transient.[89–93]
f) Activation by hormonal pathways: Candidates are progesterone, insulin, and others[94–98] but their action depends on cofactors.
g) Genetic mechanisms: There may be a large number, some associated with single nucleotide perturbations (SNPs), defects in transcription, and even lack of gene expression, expression of spice variants, to protein folding.

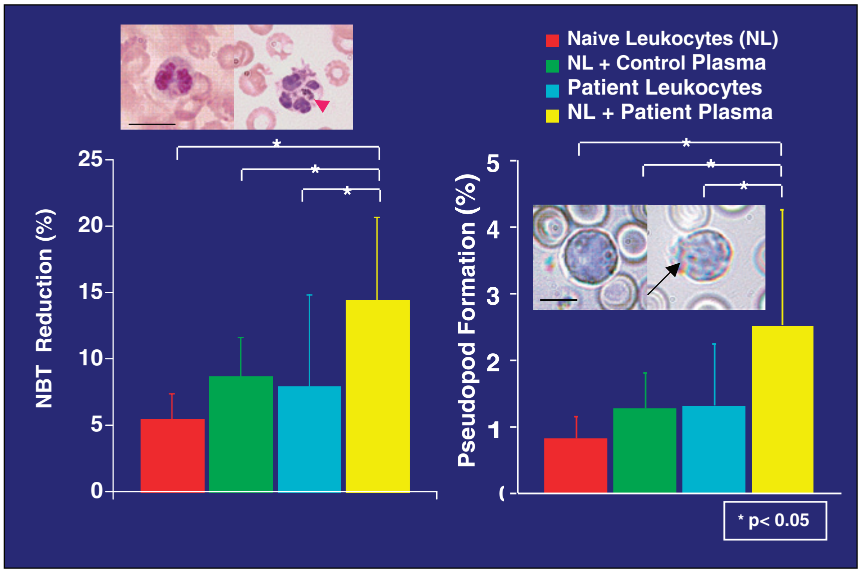

FIGURE 7.3 The plasma of (nonsmoking) patients with chronic venous disease contains an inflammatory mediator. Fraction of neutrophil activation as detected by nitroblue tetrazolium reduction to zymogen granules (left panel, red arrow) and by pseudopod projection (right panel, black arrow). Naïve leukocytes (NL) from healthy donors mixed with patient plasma has significantly higher activated neutrophil counts than either patient blood cells, healthy control cells, or patient neutrophils mixed with plasma of healthy controls. Adaped from (6). The cause of this activation is an important unresolved question in CVD.

Over the long periods of time required to develop manifestations of venous disease, it is likely that several—if not all—of these mechanisms may at one time or another stimulate inflammation in the circulation. The challenge is to identify prevailing mechanisms in chronic venous disease. Clearly, the neutrophils of patients with CVD are activated (see Figure 7.3).

A useful starting point is to look at clinically established risk factors for venous disease.[99–103] Notable in this respect are hormonal risk factors associated with pregnancy, especially in the first trimester when less effect on venous blood flow is expected, orthostatic exposure associated with a lack of blood pressure reduction due to limb movement, and enhanced body mass index have been cited in many studies. Such risks may well be associated with cell activation and in the following I will elaborate. Definitive studies have yet to be carried out.

ELEVATED BLOOD PRESSURE AND MECHANOTRANSDUCTION MECHANISMS

One of the oldest treatments for CVD is purely mechanical, a compression bandage wrapped around the diseased leg. Such compression therapy has an anti-inflammatory effect[104] although inflammatory markers require weeks of treatment[105] before a reduction of inflammation may be detectable. Although the exact mechanism is unknown, it is evident we need to consider mechanical stress.

The evidence that normal and shear stresses exerted by plasma on cell membranes may control the shape of blood vessels comes from many different observations. On one hand, there is some degree of acute control of veins and venules by passive compression of what are soft viscoelastic structures.[106] On the other hand, there is also a more chronic control by mechanical stresses of vascular structure, inflammation, and thrombosis. Indeed, the shape of even the earliest vascular plexus in the yolk sac may be controlled by fluid shear stress.[107] The formation of blood vessels and the smooth muscle media is directly influenced by both normal stress and by shear stress with synthesis of platelet-derived growth factors (PDFG-β) by endothelial cells and migration and differentiation of tissue fibroblasts.[108] Generation of an abnormal fluid flow field in otherwise healthy blood vessels within weeks can lead to major vascular remodeling, local enlargement of vessel lumen to the extreme of mature aneurysms.[109]

The venous hypertension is caused to a large degree by the lack of venous valves. Therefore outflow in proximal direction during muscle contraction in the legs is impaired and the veins become exposed to new mechanical stress. The elevated blood pressure leads to compression of the endothelium and a stretch of the venous wall, and certain locations on the veins become exposed to fluid shear stress that

is disturbed compared with normal veins and intact valves. This disturbance of the fluid shear stress is amplified further as veins change shape and stimulate an effect that profoundly affects the signaling in endothelial cells. There is now an extensive set of experiments derived in large part from endothelial cultures that show that many functions of endothelial cells are controlled by fluid shear stress (see References 110–121). Fluid shear stress is a tangential force produced by moving blood acting on the endothelial surface and a function of the velocity gradient of blood near the endothelial surface and the blood viscosity. Even though it is a small number in the circulation compared to the fluid pressure it has a powerful effect on gene expression and the pro- versus anti-inflammatory/thrombotic phenotype. Steady shear stress in a normal physiological range of about 10 dyn/cm^2 is largely anti-inflammatory, leads to orientation of the cells in the direction of the fluid flow, with extensive actin bundle (stress fiber) formation, a thick endothelium with relative low inflammatory activity, extensive attachment to the underlying extracellular matrix via focal adhesion sites and interendothelial junctions (cadherins). In contrast, low flow or flow disturbances, especially if they involve instances of reversed flow direction with forward and backward shear, cause a loss of this phenotype, and a cell that is more susceptible to inflammatory mediators. Stretch of endothelial cells and smooth muscle cells also has a direct effect on many aspects of the endothelial biology[122–127] including synthesis and release of many inflammatory molecules such as leukotrienes, prostaglandin, bradykinin, free oxygen radicals, and cytokines. Mechanical pressure of the endothelial cell (but without stretch) produces a response that is distinctly different from that of shear stress and involves growth factor release.[128,129]

Leukocytes also respond to fluid shear stress.[130] Their response is different from that of endothelial cells. If activated, they retract their pseudopods; if nonactivated, fluid shear stress induces pseudopod formation.[131] Fluid shear affects the membrane adhesion molecule distribution over the membrane of leukocytes.[132] The fluid shear stress response is influenced by the presence and concentration of inflammatory mediators in a C-GMP dependent fashion.[133] Blood flow cessation, blood stasis that implies lower shear stress, activates leukocytes as seen by projection of pseudopodia and lamellipodia and membrane attachment as the first step to transendothelial migration.

These days, blood flow in arteries is subject to detailed fluid mechanical analysis, which serves to determine the details of the flow field, pressure, and shear stress in arteries[134] and diseases like arterial aneurysms.[135–139] A comparable effort on the venous counterpart is largely missing today. Thus it is quite plausible that abnormalities in the fluid shear stress field in veins, whose diameters are distended, and whose valves have become unable to close properly, may serve as a trigger mechanism for inflammation. But the precise role of fluid stresses on blood cell and endothelial cell activation remains speculative.

PROTEASE ACTIVATION

How can an enhanced body-mass index be associated with CVD? Certainly there is a possibility that a purely mechanical mechanism may be involved with obstruction of blood flow in veins of the lower extremities in the presence of enlarged adipose deposits in the abdomen. But there are other possibilities. Recent work on inflammation in shock has brought to light that pancreatic digestive enzymes in the lumen of the intestine may serve as source for inflammatory mediators.[140–142] If digestive enzymes escape across the mucosal epithelium in the intestine and enter the wall of the intestine, self-digestion by pancreatic enzymes is initiated, and in the process fragments of extracellular matrix proteins and cells are formed that have strong pro-inflammatory properties. These pro-inflammatory fragments can enter the circulation via the portal venous circulation, but also via the intestinal lymphatics, which can diffuse directly into the peritoneal cavity. Thus the intestine can readily serve as a source of inflammatory mediators as long as there is a compromise to the usually tight permeability properties of the mucosal barrier. Thus it is interesting to note that increased intestinal permeability (measured by the lactulose/mannitol ratio technique) in patients with healed venous ulcers (class 5, CEAP) but near-normal ambulatory venous pressure can eliminate high ambulatory venous pressure as a chronic venous insufficiency risk factor.[143] This challenging observation indicates that the source for inflammation could be gut-derived, and although elevation of venous pressure, for example after loss of venous valves, will aggravate the disease process, it may not be the primary trigger mechanism. Instead a relatively innocent reduction of the intestinal barrier properties to the powerful digestive enzymes may be a source for inflammatory mediators.

GENETIC MECHANISMS

Genetic linkage analysis has brought to light that there are patients with familial risk factors. An imbalance between collagen I and collagen III has been found in proximal segments of human varicose saphenous veins in addition to fragmentation of elastin fibrils.[144] The proportion of collagen type III is significantly decreased in cultured smooth muscle cells and dermal fibroblasts derived from patients with varicose veins indicating a deficiency in collagen type III.[145] Such type of remodeling of the extracellular matrix has been proposed to be due to activation of matrix metalloproteinases (MMPs). Expression of MMP-1, MMP-2, MMP-9, and tissue inhibitor of metalloproteinases-1 has been

proposed[146,147] with a possible imbalance between these enzymes and their inhibitors.

CONCLUSION

Among the many steps that make up the inflammatory cascade in chronic venous disease, few are as important to understand as the actual trigger mechanisms. Analysis of these trigger mechanisms at the molecular lever will provide us with the tools to prevent and minimize the severity of the inflammation and may explain why the inflammatory reaction in these patients, even though inflammation is used in nature as a process for wound healing, does not come to a resolution.

Acknowledgment

I would like to thank Dr. John J. Bergan for many years of inspiring discussions and effective collaborations. Special thanks to my colleagues Drs. Luigi Pascarella, Shinya Takase, Takeshi Ono, and Alexander Penn, who carried out the experimental studies summarized in this report. Supported in part by NHLBI grant HL 42063.

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C H A P T E R

8

Chronic Venous Insufficiency: Molecular Abnormalities and Ulcer Formation

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INTRODUCTION

Chronic venous insufficiency (CVI) is a condition that affects the venous system of the lower extremities rendering the superficial, perforating, and deep veins incompetent. This results in venous hypertension causing various pathologies including pain, swelling, edema, skin changes, and ulcerations. The underlying pathology leading to CVI is a consequence of venous hypertension from valve incompetence causing venous reflux and/or obstructive disease.[1] Varicose veins by definition have incompetent valves with increased venous pressure leading to progressive dilation and tortuosity. The formation of primary varicose veins is unknown, but is likely a multifactorial process related to hereditary, female sex hormones, hydrostatic force, and hydrodynamic muscular compartments.[2] The significance of protracted venous hypertension from abnormal venous hemodynamics is the formation of dermal skin changes referred to lipodermatosclerosis, which leads to dermal and subcutaneous tissue fibrosis and eventual ulceration.[3] This chapter will review the recent literature supporting the formation of varicose veins, with specific interest in the molecular changes in the vein wall of varicosities, and basic scientific studies that have investigated the molecular alterations that are present in advanced CVI disease, namely dermal tissue fibrosis and venous ulcer formation.

VARICOSE VEINS

Abnormalities with Matrix Metalloproteinase Metabolism

Varicose veins have characteristically tortuous and dilated venous walls. A possible explanation for these findings may be the influences of proteolytic enzymes known as matrix metalloproteinases (MMPs) and their inhibitors known as tissue inhibitors of metalloproteinases (TIMPs), which lead to venous wall remodeling and subsequent dilatation and valvular incompetence. MMPs are highly homologous zinc-dependent endopeptidases that cleave most of the constituents of the extracellular matrix. To date there are 26 human MMPs that are classified according to their substrate specificity and structural similarities. The four major subgroups of MMPs are gelatinases, interstitial collagenases, stromelysins, and membrane-type matrix metalloproteinases (MT-MMPs). MMPs are important enzymes in embryogenesis, acute tissue healing, remodeling, neoplastic invasion and metastasis, skin and granulomatous diseases, aging, and chronic wounds. MMPs are regulated by cytokines, growth factors, and activation of TIMP that specifically degrade and inactivate MMPs.

In the recent decade there has been a significant interest in the role of MMPs in the pathophysiology of varicose vein formation. An early report evaluating the collagen and elastin content of nonthrombophlebitic varicose veins compared to normal saphenous veins found that there was increased collagen and a significant decrease in elastin in both varicose veins and in the vein segment not affected by valvular incompetence but with varicosities at other sites. In this study gelatin zymography and elastase activity failed to demonstrate any differences, indicating the presence of an imbalance in tissue matrix but not attributable to proteolytic activity.[4] In support of this prior study, evaluation of the vein segment at the saphenofemoral junction in patients with varicose veins demonstrated that MMPs activity was unchanged with that of control, with most of the MMPs located in the adventitia, and the content of MMP-2 was decreased but TIMP-1 content was increased.[5] Neither of

these two studies supported the role of MMPs in extracellular matrix degradation in the formation of varicose veins; however, both of these studies examined normal vein tissue in patients with varicose veins. An additional study investigated the TIMP-1/MMP-2 in varicose veins. A three-fold ratio increase was found in varicose veins compared to normal veins and the authors concluded that due to the favored proteolytic inhibition that extracellular matrix accumulation could account for the pathogenesis observed in varicose veins.[6]

To demonstrate that MMPs were induced by postural changes in patients with varicose veins, a study sampled blood from the brachial vein and lower extremity varicose vein in erect patients following 30 minutes of stasis. The investigators found that there was an abundant increase of pro-MMP-9 in the plasma of sampled blood from the varicose vein compared to arm vein. In addition, the proteolytic activity was associated with increased levels of endothelial membrane intercellular adhesion molecule-1, vascular cell adhesion molecule-1, angiotensin converting enzyme, and L-selectins indicating endothelial cell and polymorphonuclear cell activation and enzymatic granule release in varicose veins during periods of stasis.[7] This study provided evidence that MMPs are important proteolytic enzymes in patients with CVI that affect the interface of the leukocytes and endothelium in varicose veins. A number of investigators have specifically examined various MMPs in varicose veins. A current study examining MMP-1, MMP-3, MMP-13 in the proximal and distal vein segments in patients with CVI versus normal control demonstrated that transcriptional products (mRNA) were not different for MMP-1 or MMP-13 in varicose veins versus control nor in proximal versus distal varicose segments. However, the protein expression of MMP-1 was elevated in varicose veins compared to controls. In addition, regional variation of MMP-1 and MMP-13 expression were increased significantly in proximal versus distal varicose segments.[8] Other investigators have found that the morphologic variations of MMPs differ in localization by immunohistochemical technique within the endothelium, media, and adventitia, with elevated amounts of MMP-1 in smooth muscle and adventitia of varicose veins, but without any differences in TIMPs. In another study, MMP-9 was found to have increased immunopositive staining smooth muscle cells. These findings although not causative suggest that MMPs may lead to venous wall degradation and affect the extracellular matrix of the normal venous wall structure.

Of interest is whether varicose veins with concomitant thrombophlebitis have variations in MMPs expression compared to varicose veins. In a recent study evaluating MMP-1, MMP-2, MMP-3, and MMP-9 activity, it was found that thrombophlebitic varicose veins had elevated content of MMPs in the vein wall, with increased gelatinase activity and MMP-1 activity. Varicose veins had increased activity of MMP-2. It was concluded that the wall of varicose veins, especially those affected with thrombophlebitis, have extensive alterations in content and activity of MMPs that may lead to remodeling and influence venous wall mechanical properties.[9]

Alterations in Smooth Muscle Cells, Dermal Fibroblasts, and Collagen

Several studies have investigated cultured smooth muscle cells derived from varicose veins to determine if the extracellular matrix modifications seen in varicose vein tissue are related to smooth muscle cells. Smooth muscle cells cultured from varicose veins were found to have decreased number of cells staining for collagen type III and fibronectin, although the transcriptional products of these two proteins were not dissimilar. The synthesis and deposition of collagen type III but not type I was significantly lower in varicose veins. When MMPs and TIMPs were analyzed from the supernatant of confluent cells no differences were observed. These findings suggested that the regulation was altered during posttranscriptional events for both collagen type III and fibronectin in smooth muscle cells.[10] Further work in this area demonstrated that varicose greater saphenous vein has a smaller spiraled collagen distribution specifically in the intima and media.

In an interesting study, investigators evaluated cultured dermal fibroblasts collagen abnormalities, to determine if the phenotypic changes observed in venous smooth muscle cells of patients with varicose veins are also present in their dermal fibroblasts. The findings from this study demonstrated that the synthesis of collagen type I and the transcript mRNA product were increased in dermal fibroblasts, but as in smooth muscle cells, dermal fibroblasts also had decreased synthesis of collagen type III despite normal transcript. Among the various MMPs evaluated, pro-MMP-2 was increased in dermal fibroblasts cultured from patients with venous disease. The authors concluded that the synthesis of collagen type III is dysregulated in dermal fibroblasts and is comparable to the observations of smooth muscle cells derived from patients with varicose veins, suggesting a systemic alteration in tissue remodeling.[11] The same investigators demonstrated that with inhibition of MMP with Marimastat, the production of collagen type III in smooth muscle cells from varicose veins was partially restored. In addition MMP-3, which degrades fibronectin, was elevated in both transcription product and protein expression. The authors concluded that the mechanism involved in collagen type III and fibronectin degradation in the smooth muscle cells cultured from varicose veins likely is linked to the expression of MMP-3.

Alterations with Programmed Cell Death (Apoptosis)

Apoptosis involves cell suicide in response to intrinsic signals (mitochondrial pathway) or extrinsic stimuli (death receptor pathway) in order to maintain homeostasis of the organism. The intrinsic mechanism of apoptosis involves the mitochondrial pathway. In normal cells the mitochondria express the bcl-2 protein on their surface that is bound to Apaf-1 (apoptotic protease activating factor 1). Internal damage of a cell by oxygen reactive species, drugs, toxins, and radiation leads to Apaf-1 dissociation with concomitant Bax protein to enter the mitochondria with resultant cytochrome c egression in the cytosol. Cytochrome c and Apaf-1 bind to caspase 9 (cysteinyl aspartate-specific proteinase, cleave at specific aspartic acid residues), forming an apoptosome that activates other caspases that digest structural proteins and cleave chromosomal DNA causing DNA fragmentation. In the extrinsic pathway, the events that commit a cell to either a path of apoptosis or necrotic cell death after a specific stimulus is dictated in the former and not the latter by the activation of the central cell death signal via a specific set of surface death receptors that form a specific death domain effector and activate caspase 8. The specific inducers of apoptosis include tumor necrosis factor, neurotransmitters, growth factor withdrawal, IL-2 withdrawal, Fas ligands (expressed on cytotoxic T lymphocytes), whereas oxygen reactive metabolites, viral infection, chemotherapeutic drugs, radiation (UV and gamma), and toxins can affect both the intrinsic and extrinsic pathways.[12]

Alteration in apoptosis is responsible for many intractable human diseases including neurodegenerative disorders (Alzheimer's, Parkinson's), autoimmune diseases (lupus, rheumatoid arthritis), and cancer. In the past five years investigators have examined the role of apoptosis in varicose vein formation. In an earlier report the apoptotic index was 48% in control veins and only 15% in varicose veins. Apoptosis was observed only in the adventitia and immunoreactivity was similar for bcl-2 protein but cyclin D1 was increased significantly in varicose veins, indicating inhibition of apoptosis in varicose veins may be related to changes in expression of cell cycle events.[13] In further exploring the observed reduced apoptosis in varicose veins, the same authors examined the expression of bax protein and of poly ADP-ribose polymerase (PARP, involved in repair of DNA damage), which is inhibited by caspases 3 and 6 activation. In twenty patients with varicose veins, the immunoreactivity expression of bax and PARP was decreased in the distal portion of the varicose veins compared to distal control vein specimens. Both of these studies implicate that reduced apoptosis may lead to functional abnormalities required in maintaining the integrity and homeostasis of the vein wall. Other studies support the role of changes in apoptosis regulatory proteins in varicose vein pathophysiology. A recent study evaluating the distal segment of varicose veins and controls demonstrated disorganized architecture with increased collagen fibers and a decrease in the density and size of elastic fibers. In addition, varicose veins exhibited fewer immunoreactive cells in the media for bax and caspase 9, implicating that the dysregulation of the intrinsic pathway of apoptosis disrupts normal tissue integrity leading to varicose vein formation.[14]

Animal Models of Venous Hypertension

The underlying disturbance leading to varicose vein formation is venous hypertension and valvular incompetence. There are a few animal models that have investigated the effect of acute and chronic venous hypertension on molecular changes of the vein wall and valvular function. By creating a femoral artery and vein arterio-venous fistula an acute rat model of venous hypertension evaluated valvular changes and vein wall biochemical characteristics. At three weeks, three of four rats had demonstrable venous reflux and increased venous pressure (94 ± 9 mm Hg, control 11 ± 2 mm Hg) compared to the contralateral control femoral vein. The pressurized veins were dilated with valve leaflets, and length and width were reduced. There was a significant inflammatory response represented by leukocytes infiltrating the entire vein wall, and upregulation of P-selectin and intercellular adhesion molecules. In this study there were no differences in MMP-2 or MMP-9 at three weeks, and interestingly the number of apoptotic cells in the vein wall was increased.[15] In a subsequent study, these investigators evaluated both acute and chronic venous hypertension in the femoral vein of 60 rats by the same methodology. The findings were an increased pressure in the femoral vein (96 ± 9 mm Hg) with progressive reflux at 42 days post arterio-venous fistula formation. As previously determined the valves distal to the fistula demonstrated increased diameter, decreased height, and fibrosis of the valve in the media and adventitia. Of interest, valve obliteration was observed and MMP-2 and MMP-9 were elevated significantly after 21 and 42 days of venous hypertension.[16] Based on these studies, a model of venous hypertension is feasible, and significant endothelial, biochemical, and valve structure changes of inflammation and fibrosis are present. However, only proximal segments of veins were analyzed, and whether the venous changes are a result from venous hypertension, venous arterialization, or a combination will require further work to evaluate if these venous abnormalities are transmitted to distal segments of the axial veins as observed in human CVI pathology.

ADVANCED CVI: LIPODERMATOSCLEROSIS And VENOUS ULCERS

Theoretical Perspectives in CVI Dermal Fibrosis and Ulcer Formation

The formation of venous ulcer and the mechanisms for dermal fibrosis are not known. In the early 1980s and through the 1990s various investigators proposed possible explanations for the underlying cause of advanced forms of dermal pathology in CVI patients. In 41 patients with venous ulcers, tissue biopsies were stained for fibrin. The tissues were found to have layers of fibrin around dermal capillaries of lipodermatosclerotic skin, but no fibrin was found in control normal skin. The pericapillary fibrin cuff observed in skin with lipodermatosclerosis was proposed to cause tissue fibrosis and hypoxia causing ulcer formation.[17] A series of investigations on CVI patients determined that there were 24% fewer leukocytes leaving the dependent lower limb that was reversed upon elevation.[18] This led to the hypothesis that leukocytes trapped in the microcirculation (dermal capillaries) resulted in tissue ischemia and venous ulceration.[19] Growth factors are considered important mediators toward wound healing. A possible mechanism for venous ulcer formation proposed that growth factors became bound or "trapped" by macromolecules such as α-2 macroglobulin and fibrinogen.[20] The importance of these proposed theories was for further investigation to define the role of pericapillary changes, leukocyte function, and the effect of cytokines and growth factors on the pathogenesis of tissue fibrosis and venous ulcer formation.

The Role of Leukocytes

The role of leukocytes in CVI was demonstrated by the increased number of cells in the dermis of patients with lipodermatosclerosis and healed ulceration.[18] Further work in this area aimed to define cell type and function responsible for the formation of the dermal skin fibrosis and ulceration. In a study evaluating the number of white blood cells in tissue biopsies of patients with CVI, it was determined that the number of leukocytes was highest in the dermis of patients with a history of ulceration followed by tissue with lipodermatosclerosis, and lowest in patients with uncomplicated skin and CVI.[21] A careful histological study using immunohistochemistry in patients with severe lipodermatosclerotic skin changes determined that the predominant cell types were T lymphocytes and macrophages, and expression of intercellular adhesion molecule-1 was elevated but not endothelial leukocyte adhesion molecule-1 or vascular cell adhesion molecule and rarely were neutrophils observed, concluding that the accumulation of macrophages and T lymphocytes are associated with CVI skin changes and ulceration.[22] To further evaluate the activity of circulating markers on leukocytes in patients with CVI and confirm prior findings of dermal tissue histological findings, a study determined that compared to normal control patients, patients with CVI had decreased CD3+/CD38+ markers on T-lymphocytes and increased expression of CD14+/CD38+ markers on monocytes, and no neutrophil activation was present.[23] Function of mononuclear cells was evaluated by proliferation response in the presence to staphylococcal enterotoxins antigen challenge. The study concluded that mononuclear cell function deteriorated with CVI, and that diminished proliferative response was observed with greater severity of CVI disease (venous ulcers and lipodermatosclerosis), indicating that decrease mononuclear cell proliferation may be involved in poor wound healing.[24] In a quantitative study utilizing electron microscopy evaluating differences in endothelial cell structure, leukocyte cell type and their relationship to the microcirculation in dermal biopsies of patients with advanced CVI was investigated. The authors determined that patients with severe lipodermatosclerosis and healed ulcers contained a significant number of mast cells around arterioles and postcapillary venules, and in active ulcers macrophages were predominant in the postcapillary venule. Fibroblasts were the most abundant cell type in all biopsies evaluated without any differences of severity of disease, and no differences in interendothelial junctions widths were observed.[25]

The involvement of leukocytes in CVI pathology requires leukocyte/endothelial signaling for the cells to extravasate and enter the dermal tissue. A study evaluating changes in adhesion molecules in patients with severe lipodermatosclerosis and active ulceration by immunohistochemistry of biopsies adjacent to ulcerated skin demonstrated that increased expression of intracellular adhesion molecule-1 and vascular cell adhesion molecule-1 was present. In addition, the expression of leukocyte function-associated antigen-1 and very late activated antigen-4 was increased dramatically on perivascular leukocytes compared to healthy skin indicating that the upregulation of adhesion molecules in CVI patients are important mediators toward facilitating leukocyte endothelial adhesion, activation, and transendothelial migration.[26]

Although the evidence suggests that neutrophils rarely are found in the dermis of patients with severe CVI and that activation has not been detected, several studies have identified a role for neutrophils in CVI. Investigators evaluating patients with varicose veins with and without skin changes took blood samples from dependent legs in the foot in the supine position. Leukocyte surface marker CD11b and L-selectin expression were analyzed by flow cytometry, and plasma soluble L-selectin was measured by ELISA. In dependent legs with skin changes, both the median neutrophil and monocyte CD11b and L-selectin levels decreased and remained low after venous hypertension was reversed

(supine position). This also was seen in patients with uncomplicated varicose veins. The soluble L-selectin increased in the plasma in both patient groups with varicose veins during venous hypertension indicating leukocyte adhesion to the endothelium. The authors concluded that venous hypertension resulted in sequestration of activated neutrophils and monocytes in the microcirculation and persist despite removal of venous hypertension.[27] Systemic activation of leukocytes was studied in patients with lipodermatosclerosis and venous ulcers from blood samples looking at granulocyte activation with nitroblue tetrazolium reduction. There was increased neutrophil activation from patients' plasma, but not patients' whole blood, which was greater for lipodermatosclerosis and ulcer patients than those with varicose veins and edema. Their results concluded that patients' plasma may contain activating factors for granulocytes and that activated neutrophils, which were fewer in patients' whole blood than control healthy blood, which suggests that activated neutrophils in CVI patients become trapped in the peripheral circulation and may be important in the development of CVI and dermal skin changes.[28]

Alterations in Cellular Proliferation, Motility, and Regulation

Fibroblasts are an important cell in wound healing in acute and chronic wounds and, in microscopic analysis, have been determined to be a major cell type in dermal biopsies from venous ulcer and lipodermatosclerotic skin.[25] Interest in alterations in fibroblast growth and growth factor response from patients with venous ulcers was evaluated by biopsies taken from the ulcer margin and compared to normal ipsilateral thigh fibroblasts of the same patients. The authors found a significant reduction in proliferation and the fibroblasts were morphologically larger and polygonal with less uniform nuclear features. However, response to growth factors (basic fibroblast growth factor, epidermal growth factor) was maintained in venous ulcer fibroblasts, albeit not to the same magnitude of control fibroblasts. These results indicated a functional abnormality with dermal fibroblasts in venous ulcers and suggested that cellular senescence may contribute to the pathophysiology of venous ulcer formation.[29] Other investigators also have determined that venous ulcer fibroblasts have diminished proliferative rate and an attenuated response to growth factors including platelet derived growth factor (PDGF). In addition, the fibroblasts from patients with ulcers older than three years grew significantly slower than those with ulcers less than three years.[30] Certain characteristics of cellular senescence were elucidated in subsequent experiments. Venous ulcer fibroblasts contained more cells that stained positive for senescent associated-β galactosidase (specific marker for senescent state) and had increased expression of protein and mRNA product for cellular fibronectin. The authors speculated that increased accumulation of senescent cells in venous ulcers may lead to the observed impaired healing.[31] Of interest, taking ulcer fibroblasts and subjecting them to progressive passage had a significant effect on the expression of senescent associated-β galactosidase compared to normal fibroblast or fibroblasts cultured from patients with varicose veins only. Not only did the ulcer fibroblasts have an increased mean number of senescent associated-β galactosidase expressing cells (63.8 ± 8.9% vs. 11.2 ± 3.1%), but after six passages nearly all the ulcer fibroblasts were senescent (>95%). These data indicated that venous ulcer fibroblasts were significantly advanced in cellular age and closer to replicative exhaustion, suggesting that the accumulation of senescent cells in venous ulcer wounds may lead to recalcitrant healing.[32] In experiments evaluating the effect of bFGF on fibronectin and MMP-2 expression, fibroblasts from venous ulcer and CVI patients and in normal controls were found to increase the expression of these proteins. The implications were that bFGF mediated its effects by increasing both extracelluar matrix protein and matrix proteinase, indicating that the up-regulation of fibronectin and MMP-2 may be a normal, transient, and inducible response of these cells to bFGF. Furthermore, that ulcer fibroblasts at baseline have higher levels of fibronectin may not signify that they possess more of a senescent-like phenotype, but rather that they have been subjected to more mitogenic stimuli as a result of their slow growth or location in the ulcer environment.[33]

Functional studies evaluating fibroblast motility by time lapse digital photoimaging were performed in both venous ulcer fibroblasts and fibroblasts cultured from the medial malleolar skin of patients with varicose vein. The findings demonstrated a significant reduction in venous ulcer fibroblast motility compared to ipsilateral normal thigh fibroblasts and in fibroblasts from patients without any CVI, and interestingly fibroblasts from varicose vein patients also had significant lower motility. The decreased fibroblast motility was associated with the expression of α-sma a marker for myofibroblast differentiation. These data supported that altered motility in CVI fibroblasts and myofibroblast differentiation are important functional characteristics and provide further explanation in altered wound healing.[34]

The response to PDGF by venous ulcer fibroblast previously has been demonstrated to be attenuated.[30] Although these authors were unable to demonstrate any differences in PDGF receptors, a recent report demonstrated that venous ulcer fibroblasts had no growth response to PDGF AB, and the basal levels of PDGF α and PDGF β receptors were decreased.[35] A possible explanation for these differences is that in the latter, fibroblasts were cultured from biopsies taken from the ulcer margin,[35] and in the former, biopsies were from the central portion of granulation tissue and from lipodermatosclerotic skin.[30]

The regulatory mechanisms for fibroblast-reduced growth and attenuated response to growth factors remain unknown. In a recent report the mitogen-activated protein kinase pathway (MAPK) ERK1 and -2 were studied in venous ulcer fibroblasts treated with PDGF AB. The ulcer fibroblasts were found to activate MAPK and inhibition of the upstream kinase MEK1 significantly reduced fibroblast proliferation, which was reversible with the addition of PDGF. In addition venous ulcer wound fluid inhibited MAPK directly. These data suggest the importance of the MAPK ERK pathway in regulating venous ulcer fibroblasts proliferation.[36]

Key cell-cycle regulatory proteins for proliferation and apoptosis specifically involved with epithelialization have been investigated. In biopsies of venous ulcers, diabetic ulcers, and control subjects no major differences in keratinocyte immunohistochemical staining was observed for cell-cycle regulatory proteins or apoptosis-related proteins.[37] In a follow-up study these investigators compared the edge of venous ulcer to that of the central granulation tissue for growth factors and cytokines in keratinocytes and endothelial cells by immunohistochemistry and phenotype characterization. Significant findings were that on the ulcer margin, keratinocytes and endothelial cells retained their secretory potential for growth factors and cytokines, whereas the ulcer bed was significant for very few fibroblasts and mainly scavenging cells (macrophages) presence.[38] From these data the authors speculated that the wound bed organization was altered by chronic infections, and impaired nutrition inhibited keratinocyte migration. It is well known that fibronectin is an important protein of the extracellular matrix and involved in keratinocyte reepithelialization. A study evaluating biopsies from venous ulcer wound margin, acute wounds, and normal skin determined that the transcription product for fibronectin was increased significantly in venous ulcer. However, immunostaining for alpha5beta1 integrin, the cell surface receptor for fibronectin, was undetectable in venous ulcer biopsies. The authors concluded that although fibronectin mRNA was expressed, the lack of integrin receptor may prevent keratinocyte migration and wound closure.[39]

Alterations in Transforming Growth Factor Function

Transforming growth factor beta1 (TGF-β1) is an important growth factor with functional properties in regulating cell proliferation, extracellular matrix production, and immunosuppressive effects. A number of investigators have studied the role of TGF in patients with venous ulcer and lipodermatosclerotic skin changes. In an immunohistochemical study of venous ulcer and normal skin graft donor sites, in the venous ulcer biopsies there was increased α-2 macroglobulin, increased number of type I procollagen fibroblasts, and elevated immunoreactivity of TGF-β1 within fibrin cuffs but not in the provisional matrix of the ulcer bed around the cuffs. In comparison, normal skin had restriction of α-1 macroglobulin to the vessel lumen, and procollagen and TGF-β1 were present within the granulating matrix and adjacent to the wound margin. These data suggested that although TGF is present in venous ulcers it is distributed in the fibrin cuff and not available in the wound matrix due to binding by α-2 macroglobulin.[40] The responsiveness of venous ulcer fibroblasts to TGF was tested. Investigation determined that ulcer fibroblasts compared to normal fibroblasts at baseline had the same capacity for procollagen synthesis by tritiated proline incorporation assay, and no difference was detected in total TGF-β1 synthesis. As well, similar mRNA levels of α-1 procollagen and TGF-β1 were present. In exogenously TGF-β1–stimulated fibroblasts, venous ulcer fibroblasts failed to increase collagen production and were associated with a four-fold decrease in TGF-β type II receptors.[41] Other investigation with CVI patients evaluated lipodermatosclerostic skin, healed ulcers, and active ulcers. Compared to control skin, the transcriptional product for TGF-β1 was elevated only in lipodermatosclerotic biopsies, and total TGF-β1 protein was increased in all CVI specimens and significantly higher in biopsies closer to the diseased skin than the thigh. Immunohistochemical examination of TGF-β1 localized the protein to the epidermis, fibroblasts, and leukocytes, which appeared to be mast cells; in contrast normal skin had TGF-β1 present only in the epidermis. The authors concluded that fibroblasts are target cells that are activated by leukocytes, and that alterations in tissue remodeling leads to fibrosis in patients with advanced CVI.[42] Evaluation of fibroblast response to TGF-β1 was performed in early (C2 and C3) and late stages (C4–6) of CVI, and the composition of the extracellular matrix tissue cultures was tested for proliferative effect of TGF-β1 treated fibroblasts. Response to TGF-β1 was normal in C2 and C3 CVI fibroblast, with diminished proliferation of C4 that was reversible in TGF-β1 treated cells. In C5 and C6 fibroblasts TGF-β1 was unable to cause any increase in proliferation. Changing the composition of the extracellular matrix from polystyrene, collagen, or fibronectin had no effect in increasing TGF-β1 treated advanced CVI fibroblasts.[43]

Recent investigations on the mechanisms of fibroblasts unresponsive to TGF-β1 from venous ulcer and lipodermatosclerotic skin have been evaluated. A previous study demonstrated that the TGF-β type II receptors were lower.[41] A recent study of venous ulcer fibroblasts determined that the transcript for TGF-β type II receptors and number of receptors was decreased. Decreased receptor expression was associated with inhibited phosphorylation of Smad 2 and 3 proteins and MAPK ERK 1 and 2, which are important downstream cell regulatory kinases that are phosphorylated in response to TGF-β type II receptor activation by ligand.

These findings indicate abnormal signaling pathways that may be responsible for altered fibroblast proliferation in venous ulcers.[44]

Alterations in Extracellular Remodeling and the Wound Fluid Environment

The extracellular matrix (ECM) is an important structural and functional scaffolding made up of proteins that are necessary for cell function, wound repair, epithelialization, blood vessel support, cell differentiation and signaling, and cellular migration. The ECM is particularly important in providing a substrate for keratinocytes to migrate and establish coverage in both acute and chronic wounds.[39] Alterations in protease activity and the relation to abnormalities in ECM metabolism in wounds have been areas of active investigation in the past decade. In an early report evaluating wound fluid collected from patients with venous ulcers, the investigators determined that compared to acute wound fluid, the chronic wound fluid contained up to ten-fold increased levels of MMP-2 and MMP-9 as well as increased activity of the enzymes, suggesting high tissue turnover.[45] Increased MMP-1 and gelatinase activity from the exudates of chronic venous leg ulcers also has been confirmed by other investigators, and the doxycycline inhibition studies suggested that the protease activity was that of fibroblasts, mononuclear cells, keratinocytes, or endothelial cells and not neutrophils.[46] It is important to note that MMP's levels and activity, although abnormal in venous ulcers, is not specific to just venous disease, and alterations are found in other inflammatory wounds including burn and pressure ulcers.[47] The excess proteolytic activity in venous leg ulcers has been found to degrade essential plasminogen, which is important in activating pro-MMP to MMP necessary for fibrinolysis and cell migration, and MMP's inhibit plasmin production by keratinocytes, which may lead to reduced cell migration.[48] Of interest, a study evaluating fibroblasts cultured from venous ulcers determined that there was a marked reduction in MMP-1 and MMP-2 level and activity, and a significant increase in TIMP-1 and TIMP-2 production. The authors concluded that the inhibition of proteinase activity by TIMP in fibroblasts causes impaired function to reorganize the ECM in chronic wounds leading to delayed healing.[49]

The abnormalities in structure and healing process seen in lipodermatosclerotic skin have also been attributed to MMP pathophysiology. A study where dermal biopsies were obtained from liposclerotic skin and compared to healthy skin and analyzed by immunohistochemistry, reverse transcriptase polymerase chain reaction, immunoblot, and zymography found that lipodermatosclerotic skin had increased expression of mRNA and protein for MMP-1, MMP-2, and TIMP-1, and increased levels of active MMP-2. The MMP-2 was localized predominantly in the basal and suprabasal layers of the epidermis, perivascular region, and reticular dermis, and had less TIMP-2 in the basement membrane of the diseased skin. The relevance of this study was that lipodermatosclerotic skin is characterized by elevated ECM turnover.[50] The regulation of MMP production is complex. Posttranslational modifications of MMPs appear to be essential, and dermal fibroblasts and leukocytes are sources for MMPs, especially MMP-2, and likely regulated by TGF-β1.[51] The interplay of MAPK with MMP activation has also been investigated in fibroblasts. The cytokine tumor necrosis factor alpha has been demonstrated to induce MMP-19 expression, which is inhibited by blocking MAPK pathways ERK1 and ERK2 with PD98059 and p38 with SB203580. In addition, adenovirus mediated induction of ERK 1 and ERK 2 in combination with p38 resulted in potent MMP-19 expression in fibroblasts and the activation of c-JNK also produced abundant pro-MMP-19. These data indicated the important regulatory functions of MAPK and proteolytic activity in dermal fibroblasts.[52]

The venous ulcer microenvironment consists of dermal fibroblasts, keratinocytes, inflammatory cells, ECM, bacteria, and microcirculation. An interesting aspect of the venous ulcer milieu is the presence of the chronic wound fluid. The wound fluid is known to have properties of excess protease activity as stated earlier. In addition, the venous ulcer wound fluid has been demonstrated to cause inhibition of fibroblast proliferation and induce changes of cellular senescence.[34,53] The venous ulcer wound fluid has been demonstrated to inhibit the growth of fibroblasts with the majority of cells with a G1 and G2 DNA content in the cell cycle (quiescent state, unable to enter S phase). Proliferation of fibroblasts treated with chronic venous ulcer wound fluid could be reestablished by heat inactivation or reversed by removal and placement of cells in 10% serum.[54] In addition to fibroblasts, wound fluid from venous ulcers also inhibits the proliferation of endothelial cells and keratinocytes. Although the inhibitory component(s) and the responsible source(s) for production of wound fluid are not known, the active inhibitory substance can be fractionated and consist of a molecular weight of less than 30 kd.[55] In neonatal fibroblasts, venous ulcer wound fluid was demonstrated to inhibit the expression of MAPK, specifically ERK 1 and ERK 2, with simultaneous decrease in proliferation.[36] In addition, the mechanism of cell inhibition by wound fluid, in part, involves downregulation of phosphorylated retinoblastoma tumor suppression gene and cyclin D1, via inhibition of Ras-dependent MAPK pathway.[56]

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C H A P T E R

9

Pathophysiology of Chronic Venous Insufficiency

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INTRODUCTION

Ten to 35% of adults in the United States have some form of chronic venous insufficiency (CVI), with venous ulcers affecting 4% of people over the age of 65.[1,2] Due to the high prevalence of the disease, the population-based costs to the U.S. government for CVI treatment and venous ulcer care has been estimated at over one billion dollars a year. In addition, 4.6 million work days per year are lost to venous-related illnesses.[3,4] The recurrent nature of the disease, the high cost to the health care system, and the ineffectiveness of current treatment modalities underscore the need for CVI-related research. The past decade has further defined the role of leukocyte-mediated injury and elucidated the role of inflammatory cytokines in lower extremity dermal pathology. In addition, several laboratories have performed investigations on pathologic alterations in cellular function and the molecular regulation of these processes observed in patients with CVI. This chapter will discuss the pathophysiology of varicose vein formation and the molecular regulation of inflammatory damage to the lower extremity dermis caused by persistent ambulatory venous hypertension.

VARICOSE VEIN FORMATION (MACROSPCOPIC ALTERATIONS)

Genetics and the Role of Deep Venous Thrombosis (DVT)

Unlike arteries, veins are thin-walled, low pressure conduits whose function is to return blood from the periphery to the heart. Muscular contractions in the upper and lower extremities propel blood forward and a series of intraluminal valves prevent retrograde flow or reflux. Venous reflux is observed when valvular destruction or dysfunction occurs in association with varicose vein formation. Valvular reflux causes an increase in ambulatory venous pressure and a cascade of pathologic events that manifest themselves clinically as lower extremity edema, pain, itching, skin discoloration, varicose veins, venous ulceration, and, in its severest form, limb loss. These clinical symptoms collectively refer to the disorder known as chronic venous insufficiency (CVI).[5] Age, gender, pregnancy, weight, height, race, diet, bowel habits, occupation, posture, previous deep venous thrombosis, and genetics all have been proposed as predisposing factors associated with varicose vein formation. Except for previous deep vein thrombosis and genetics, there is poor evidence that indicates a causative relationship between these predisposing factors and the formation of varicose veins. Refer to Kevin Burnand's textbook, *Diseases of the Vein*, for further discussion on these predisposing factors.[6]

There are few reported epidemiologic investigations that suggest a relationship between varicose vein formation and a genetic predisposition.[7,8] It was previously thought that axial destruction of venous valves led to transmission of ambulatory venous hypertension causing reflux and varix formation.[6] However, a publication by Labropoulos et al. indicated that the most frequent location for initial varicose vein formation was in the below-knee greater saphenous vein (GSV) and its tributaries, followed by the above-knee GSV, and the saphenofemoral junction.[9] This study clearly indicates that vein wall degeneration with subsequent varix formation can occur in any segment of the superficial and deep systems at any time and suggests a genetic component to the disease. In 1969, Gunderson and Hauge reported on the epidemiology of varicose veins observed in the vein

clinic in Malmo, Sweden, over a two-month period.[7] Of 250 patients, 154 female and 24 male patients provided complete survey information on their parents and siblings. Although biased by the predominance of women and dependence on survey data, this report suggested that patients with varicose veins had a higher likelihood of developing varicosities if their fathers had varicose veins. Furthermore, the risk of developing varicose veins increases if both parents had varicosities. Cornu-Thenard et al. prospectively examined 67 patients and their parents. Patients' nonaffected spouses and parents were used as controls for a total of 402 subjects.[8] These investigators reported that the risk of developing varicose veins was 90% when both parents were affected, 25% for males, and 62% for females if one parent is affected and 20% when neither parent is affected. These data suggest an autosomal dominant with variable penetrance mode of genetic transmission. The decreased incidence in males with an affected parent and the spontaneous development in patients without affected parents suggests that males are more resistant to varix formation and that other multifactorial etiologies in patients with predispositions to the disease must exist. To further elucidate the genetic component of the disease, molecular analyses with gene chip technologies is required. The chromosome responsible for the disease and its protein by products are currently unknown.

An injury to the venous endothelium or local procoagulant environmental factors leads to thrombus formation in the venous system. It is currently well accepted that a venous thrombus initiates a cascade of inflammatory events that contributes to or causes vein wall fibrosis.[10] Thrombus formation at venous confluences and valve pockets leads to activation of neutrophils and platelets. Activation of these cells leads to formation of inflammatory cytokines, procoagulants, and chemokines leading to thrombin activation and further clot formation. Production of inflammatory mediators creates a cytokine/chemokine gradient leading to leukocyte invasion of the vein wall at the thrombus wall interface and from the surrounding adventitia. Up-regulation of adhesion molecules perpetuates this process, eventually leading to vein wall fibrosis, valvular destruction, and alteration of vein wall architecture.[10,11] Although the mechanisms associated with vein wall damage secondary to venous thrombosis are beginning to be unraveled, the majority of varicose veins occurs in patients with no prior history of deep venous thrombosis. The etiology of primary varicose veins continues to be a mystery.

Vein Wall Anatomy, Histopathology, and Functional Alterations

Whatever the initiating event, several unique anatomic and biochemical abnormalities have been observed in patients with varicose veins. Normal and varicose greater saphenous veins (GSVs) are characterized by three distinct muscle layers within their walls. The media contains an inner longitudinal and an outer circular layer, and the adventitia contains a loosely organized outer longitudinal layer.[12–14] In normal GSVs, these muscle layers are composed of smooth muscle cells (SMCs), which appear spindle-shaped (contractile phenotype) when examined with electron microscopy (see Figure 9.1).[15] These cells lie in close proximity to each other, are in parallel arrays, and are surrounded by bundles of regularly arranged collagen fibers. In varicose veins, the orderly appearance of the muscle layers of the media is replaced by an intense and disorganized deposition of collagen.[15–17] Collagen deposits separate the normally closely opposed SMCs and are particularly striking in the media. SMCs appear elliptical rather than spindle-shaped, and demonstrate numerous collagen-containing vacuoles imparting a secretory phenotype (see Figure 9.2).[15] What causes SMCs to dedifferentiate from a contractile to a secretory phenotype is currently unknown. Ascher et al. theorized that SMC dedifferentiation may be related to dysregulation of apoptosis.[18,19] These investigators reported a decrease in the proapoptotic mediators bax and PARP (Poly ADP-ribose polymerase) in the adventitia of varicose veins compared to normal veins. Although no difference in these mediators was observed in the media or intima of varicose veins, a decrease in SMC turnover was postulated as a possible cause for the increase in secretory phenotype. Increased phosphorylation of the retinoblastoma protein, an intracellular regulator of cellular proliferation and differentiation, has been observed in varicose veins, and may similarly contribute to this process.[13]

FIGURE 9.1 Electron micrograph of normal greater saphenous vein (Mag 11,830×). Note organized structure of alternating smooth muscle cells (long arrows) with spindle-shaped contractile phenotype, interspersed by longitudinally arranged collagen bundles (short arrows).

Vein wall remodeling has been observed consistently in histologic varicose vein specimens.[12,14–17,20] Gandhi et al. quantitatively demonstrated an increase in collagen content and a decrease in elastin content compared to normal GSVs.[20]

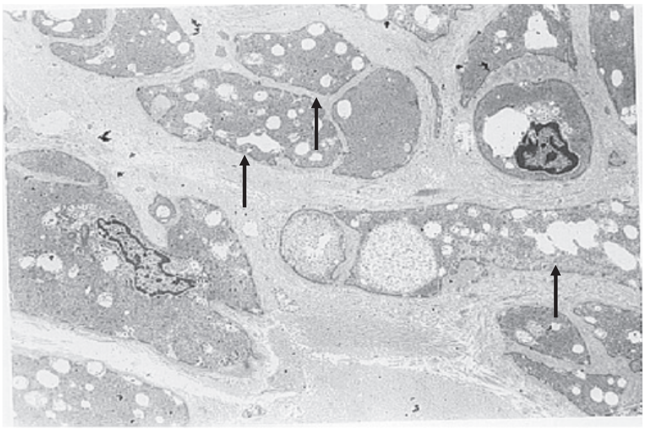

FIGURE 9.2 Electron micrograph of varicosed greater saphenous vein (Mag 4240×). Smooth muscle cells exhibit prominent vacuoles (arrows) and an elliptical appearance consistent with a secretory phenotype. Smooth muscle cells are separated by diffusely deposited collagen bundles which impart a disorganized architectural appearance to the vein wall.

The net increase in the collagen/elastin ratio suggested an imbalance in connective tissue matrix regulation. As a result, several investigators have observed alterations in matrix metalloproteinase and fibrinolytic activity in varicose veins. TIMP-1 and MMP-1 protein levels are increased at the saphenofemoral junction compared to normal controls, whereas MMP-2 levels are decreased.[21] No overall differences in MMP-9 protein or activity levels have been identified, however, the number of cells expressing MMP-9 by immunohistochemistry has been reported to be elevated in varicose veins compared to normal veins.[22,23] There are conflicting reports regarding the role of plasmin activators and their inhibitors. Shireman et al. reported that uPA (urokinase plasminogen activator) levels are increased three to five times compared to normal controls in the media of vein specimens cultured in an organ bath system.[24] No differences were noted in tPA (Tissue Plasminogen Activator) or PAI-1 (Plamin Activator Inhibitor-1) levels. However, other investigations have reported a decrease in uPA and tPA activity by enzyme zymography in varicose veins.[22,25] These data suggest that the plasminogen activators may play a role in matrix metalloproteinase activation leading to vein wall fibrosis and varix formation; however, further research into the mechanisms regulating vein wall fibrosis clearly are needed.

What effect vein wall fibrosis has on venous function needs further elucidation. The contractile responses of varicose and normal GSV rings to noradrenaline, potassium chloride, endothelin, calcium ionophore A23187, angiotensin II, and nitric oxide have been evaluated by several investigators.[26,27] These studies have demonstrated decreased contractility of varicose veins when stimulated by noradrenaline, endothelin, and potassium chloride. Similarly, endothelium dependent and independent relaxations after A23187 or nitric oxide administration were diminished compared to normal GSVs, respectively. The mechanisms responsible for decreased varicose vein contractility appear to be receptor mediated.[27,28] Utilizing Sarafotoxin S6c (selective pharmacologic inhibitor of endothelin B) and competitive inhibition receptor assays with ^{131}I-endothelin-1, a decrease in endothelin B receptors have been observed in varicose veins compared to normal GSVs.[28] Feedback inhibition of receptor production secondary to increased endothelin-1 is postulated to mediate the decreased receptor content in varicose vein walls. Other possible mechanisms for decreased contractility appear related to cAMP levels and the ratio of prostacyclin to thromboxane-A2.[29] Cyclic-AMP is increased in varicose vein specimens compared to normal GSVs. In addition, the ratio of prostacyclin to thromboxane-A2 is increased even though absolute protein levels do not differ between normal veins and varicosities. Whether venodilation of varicosities is caused by diminished endothelin receptor levels and responsiveness to cAMP or by a secondary effect of varix formation is not known. However, it is clear that with the development of vein wall fibrosis, varicose veins demonstrate decreased contractile properties that probably exacerbate the developement of ambulatory venous hypertension.

HISTORICAL THEORIES

In the twentieth century numerous theories have been postulated regarding the etiology of CVI and the cause of venous ulceration. The venous stasis, arteriovenous fistula, and diffusion block theories have been disproven over time and are discussed here for historical interest only. The etiology for dermal skin pathology is primarily a chronic inflammatory process and the events regulating these events are discussed later.

Venous Stasis Theory

In 1917, John Homans published a manuscript entitled "The etiology and treatment of varicose ulcer of the leg," in *Surgery, Gynecology and Obstetrics*.[30] This manuscript was a clinical treatise on the diagnosis and management of patients with CVI. In this manuscript Dr. Homans coined the term *post-phlebitic syndrome* and speculated on the cause of venous ulceration. He stated that "Overstretching of the vein walls and destruction of the valves upon which the mechanism principally depends bring about a degree of surface stasis which obviously interferes with the nutrition of the skin and subcutaneous tissues. . . . It is to be expected, therefore that skin which is bathed under pressure in stagnant venous blood will readily form permanent, open sores or ulcers."[30] This statement resulted in a generation of

investigators trying to seek a causal relationship between hypoxia, stagnant blood flow, and the development of CVI.

The first investigator to address the question of hypoxia and CVI scientifically was Alfred Blalock.[31] He obtained venous samples from the femoral, greater saphenous, and varicose veins in 10 patients with CVI isolated to one limb and compared their oxygen content to samples taken from corresponding veins in the opposite limb. Seven of the patients had active ulcers at the time. All samples were collected in the recumbent and standing positions. He reported that in patients with unilateral CVI the oxygen content was higher in the femoral vein of the affected limb. He speculated that this observation may be reflective of increased venous flow rather than stagnation.

Arteriovenous Fistula Theory

The concept of increased venous flow in the dermal venous plexus was expanded upon by Pratt who reported that increased venous flow in patients with CVI could be clinically observed.[32] He attributed the development of venous ulceration to the presence of arteriovenous connections and coined the term *arterial varices*. He reported that in a series of 272 patients with varicose veins who underwent vein ligation, 24% had arteriovenous connections. Of the 61 patients who developed recurrences, 50% occurred in patients with arteriovenous communications identified clinically by the presence of arterial pulsations in venous conduits. Pratt hypothesized that increased venous flow shunted nutrient and oxygen rich blood away from the dermal plexus leading to areas of ischemia and hypoxia and resulting in venous ulceration. Pratt's clinical observations however, have never been confirmed with objective scientific evidence. Experiments with radioactively labeled microspheres have never demonstrated shunting and have therefore cast serious doubts on the validity of this theory.

Diffusion Block Theory

Hypoxia and alterations in nutrient blood flow again were proposed as the underlying etiology of CVI in 1982 by Burnand et al.[33] These authors performed a study in which skin biopsies were obtained from 109 limbs of patients with CVI and 30 limbs from patients without CVI. Foot vein pressures were measured in the CVI patients at rest and after 5, 10, 15, and 20 heel raises. Vein pressure measurements were then correlated with the number of capillaries observed on histologic section. The authors reported that venous hypertension was associated with increased numbers of capillaries in the dermis of patients with CVI. Whether the histologic sections represented true increases in capillary quantity or an elongation and distension of existing capillaries was not answered by this study. However, in a canine hind limb model, the authors were able to induce enlargement in the number of capillaries with experimentally induced hypertension.[34] This important investigation was one of the first studies to demonstrate a direct effect of venous hypertension on the venous microcirculation. In a later study, Browse and Burnand noted that the enlarged capillaries observed on histologic examination exhibited pericapillary fibrin deposition and coined the term *fibrin cuff*.[35] They speculated that venous hypertension led to widening of endothelial gap junctions with subsequent extravasation of fibrinogen leading to the development of fibrin cuffs. These authors theorized that the cuffs acted as a barrier to oxygen diffusion and nutrient blood flow, resulting in epidermal cell death. Although pericapillary cuffs do exist, it has never been demonstrated that they act as a barrier to nutrient flow or oxygen diffusion.

LEUKOCYTE ACTIVATION

Dissatisfaction with the fibrin cuff theory and subsequent observations of decreased circulating leukocytes in blood samples obtained from the greater saphenous veins in patients with CVI led Coleridge Smith and colleagues to propose the leukocyte trapping theory.[36] This theory proposes that circulating neutrophils are trapped in the venous microcirculation secondary to venous hypertension. The subsequent sluggish capillary blood flow leads to hypoxia and neutrophil activation. Neutrophil activation leads to degranulation of toxic metabolites with subsequent endothelial cell damage. The ensuing heterogenous capillary perfusion causes alterations in skin blood flow and eventual skin damage. The problem with the leukocyte trapping theory is that neutrophils have never been directly observed to obstruct capillary flow, therefore casting doubt on its validity. However, there is significant evidence that leukocyte activation plays a major role in the pathophysiology of CVI.

ROLE OF LEUKOCYTE ACTIVATION AND FUNCTIONAL STATUS IN CVI

In 1988, Thomas et al. reported that 24% fewer white cells left the venous circulation after a period of recumbency in patients with CVI as compared to normal patients.[37] They studied three groups of 10 patients each. Group 1 consisted of patients with no signs of venous disease. Group 2 were patients with uncomplicated primary varicose veins, and group 3 were patients with long-standing CVI as determined by Doppler ultrasonography, strain-gauge plethysmography, and foot volumetry. Patients had the greater saphenous vein cannulated just above the medial malleolus. Venous samples were obtained at various time points with patients in the sitting and supine position. Samples were then placed in an automated cell counter and the number of leukocytes and

erythrocytes determined. The ratio of white cells to red cells at the various time points, were then compared. The authors reported that with leg dependency, packed cell volume significantly increased in patients with CVI as compared to normal controls whereas patients with primary varicose veins showed no difference from controls. They also noted that the relative number of white cells were significantly decreased compared to control and primary varicose vein patients (28% vs 5%, $p < 0.01$). The authors concluded that the decrease in white cell number was due to leukocyte trapping in the venous microcirculation secondary to venous hypertension. They further speculated that while trapped, leukocytes may be activated and release toxic metabolites causing damage to the microcirculation and the overlying skin. These important observations were the first to implicate abnormal leukocyte activity in the pathophysiology of CVI.

The importance of leukocytes in the development of dermal skin alterations was empahsized by Scott et al.[38] These authors obtained punch biopsies from patients with primary varicose veins, lipodermatosclerosis, and patients with lipodermatosclerosis and healed ulcers, and determined median number of white blood cells (WBCs) per high power field (40× magnification) in each group. No patients with active ulcers were included and no attempt to identify the type of leukocytes was made. The authors reported that in patients with primary varicose veins, lipodermatosclerosis, and healed ulceration there was a median of 6, 45, and 217 WBCs per mm^2, respectively. This study demonstrated that with clinical disease progression and increasing severity of CVI, there was a progressive increase in the number of leukocytes in the dermis of CVI patients.

The types of leukocytes involved in dermal venous stasis skin changes are controversial. In a study performed by Wilkerson et al., skin biopsies were obtained from 23 patients who required surgical ligation, stripping, and/or avulsion for their varicose veins.[39] The condition of the skin was recorded as liposclerotic, eczematous, or normal. Lipodermatosclerosis was defined clinically as palpable induration of the skin and subcutaneous tissues and eczema as visible erythema with scaling of the skin. Using immunohistochemical techniques, the authors stained for leukocyte-specific cell surface markers and reported that macrophages and lymphocytes were the predominant leukocytes observed in this patient population. Neutrophils and B-lymphocytes rarely were observed. T-lymphocytes and macrophages were predominantly observed perivascularly and in the epidermis. However, Pappas et al. performed a quantitative morphometric assessment of the dermal microcirculation using electron microscopy and reported that macrophages and mast cells were the predominant cells observed in patients with CVI dermal skin changes.[40] Furthermore, lymphocytes were never observed. This discrepancy may reflect the types of patients that were studied. Wilkerson et al. biopsied patients with erythematous and eczematous skin changes, whereas Pappas predominantly evaluated older patients with dermal fibrosis. Patients with eczematous skin changes may have an autoimmune component to their CVI, whereas patients with dermal fibrosis may reflect changes consistent with chronic inflammation and altered tissue remodeling.

Given the predominant role of leukocytes in CVI pathology, there has been great interest in the activation state and functional status of leukocytes in CVI patients. Pappas et al. explored the hypothesis that circulating leukocytes in CVI patients were in an altered state of activation and therefore may be involved in leukocyte-mediated injury. They measured the expression of cell surface activation markers of circulating leukocytes using fluorescence flow cytometry.[41] Relative to normal individuals, patients with chronic venous stasis ulcers had a decreased expression of the CD3+/DR+ and CD3+/CD38+ markers on T-lymphocytes and an increased expression of CD14+/CD38+ markers on monocytes. Circulating neutrophils demonstrated no evidence of activation.

Although Pappas et al. identified a population of circulating cells demonstrating altered activation markers their results did not test the functional status of these cells. In a follow-up study, Pappas et al. tested the hypothesis that circulating mononuclear cells in CVI patients were dysfunctional by challenging monocytes with test mitogens.[42] Lymphocyte and monocyte cell function was measured as the degree of proliferation in response to a mitogenic challenge. Fifty patients were separated into four groups: Group 1, 14 patients with normal limbs; Group 2, 10 patients with class II CVI (stasis dermatitis only); Group 3, 15 patients with active venous ulcers; Group 4, 11 patients with healed venous ulcers and current evidence of lipodermatosclerosis. Systemically circulating lymphocytes and monocytes were obtained by antecubital venipuncture from Groups 1–4. Cells were cultured in the presence of staphylococcal enterotoxins (SEs) A, B, C_1, D and E (mitogens) and PHA, a control mitogen (Phytohemagglutinin). Proliferative responses to PHA indicated that lymphocytes and monocytes from CVI patients were not globally depressed. However, patients in Group 2 did not exhibit the same degree of proliferation to PHA as did Groups 1, 3, and 4. Differences in proliferative responses between Goup 2 and 1 (44.38 ± 43.9 versus 118.87 ± 27.1, $p < 0.05$) and Groups 2 and 3 (44.38 ± 43.9 versus 105.95 ± 60.99, $p < 0.05$) were significant. Challenges with staphylococcal enterotoxin A and B revealed significant diminution of proliferative responses in Groups 2 (42.73 ± 11.55, $p < 0.05$) and 3 (45.57 ± 9.1, $p < 0.05$) and Groups 3 (36.81 ± 6.9, $p < 0.05$) and 4 (35.04 ± 7.5, $p < 0.05$), compared to SEA controls (68.68 ± 9.9) and SEB controls (66.25 ± 13.56), respectively. A trend toward diminished cellular function with progression of CVI was observed with staphylococcal enterotoxins B, C_1, D, and

E, strongly suggesting biologic significance. Furthermore, patients with LDS and a history of healed ulcers uniformly exhibited the poorest proliferative responses. This study indicated that deterioration of mononuclear cell function was associated with CVI and suggested that lymphocyte and monocyte function diminished with clinical disease progression. The authors speculated that the decreased capacity for mononuclear cell proliferation in response to various challenges may manifest itself clinically as poor and prolonged wound healing.

THE VENOUS MICROCIRCULATION

Numerous investigations have attempted to evaluate the microcirculation of patients with CVI.[40,43–46] The majority of these investigations were qualitative descriptions of vascular abnormalities, which lacked uniformity of biopsy sites and patient stratification. Prior to 1997 it was widely accepted that endothelial cells from the dermal microcirculation appeared abnormal, contained Weibel-Palade bodies, were edematous, and demonstrated widened interendothelial gap junctions.[45] Based on these descriptive observations it was assumed that the dermal microcirculation of CVI patients have functional derangements related to permeability and ulcer formation. It was not until 1997 that a quantitative morphometric analysis of the dermal microcirculation was reported.[40] The objectives of this investigation were to quantify differences in endothelial cell structure and local cell type with emphasis on leukocyte cell type and their relationship to arterioles, capillaries, and post-capillary venules (PCVs). Variables assessed were number and types of leukocytes, endothelial cell thickness, endothelial vesicle density, interendothelial junctional width, cuff thickness, and ribosome density. Thirty-five patients had two four-millimeter punch biopsies obtained from the lower calf (gaiter region) and lower thigh. Patients were separated into one of four groups according to the 1995 ISCVS/SVS (International Society for Cardiovascular Surgery/Society for Vascular Surgery) CEAP classification.[5] Group 1 consisted of five patients with no evidence of venous disease. Skin biopsies from these patients served as normal controls. Groups 2 through 4 consisted of patients with CEAP Class 4 (n = 11), Class 5 (n = 9), and Class 6 (n = 10) CVI.

ENDOTHELIAL CELL CHARACTERISTICS

No significant differences were observed in endothelial cell thickness of arterioles, capillaries, and PCVs from either gaiter or thigh biopsies.[40] Qualitatively, endothelial cells appeared metabolically active. Many nuclei exhibited a euchromatic appearance, implying active mRNA transcription. In most instances ribosome numbers were so abundant that they exceeded the resolution capacity of the image analysis system and were unable to be quantified. The prominence in ribosome content and the euchromatic appearance of the endothelial cell nucleus strongly suggested active protein production. No significant differences in vesicle density were observed in gaiter biopsies between groups. Class 6 patients exhibited an increased number of vesicles in arterioles and PCV endothelia from thigh biopsies but did not differ compared to gaiter biopsies. Mean interendothelial junctional width varied within a normal range of 20–50 nm. Significantly widened interendothelial gap junctions were not observed and thus conflicted with the reports of Wenner et al.[45] Mean basal lamina thickness differed significantly at the capillary level in both gaiter and thigh biopsies. Differences were most pronounced in patients with Class 4 disease. These data indicated that endothelial cells from the dermal microcirculation of CVI patients were far from normal. They demonstrated increased metabolic activity suggestive of active cellular transcription and protein production. Most surprising was the observation of uniformly tight gap junctions. Previously these gap junctions were reported to be as wide as 180 nanometers and it was assumed that these widened junctions were responsible for macromolecule extravasation and edema formation.[33,45] Pappas et al. suggested that alternate methods for tissue edema like increased transendothelial vesicle transport, formation of transendothelial channels, and alterations in the glycocalyx lining the junctional cleft may be involved in CVI edema and macromolecule transport.[40]

TYPES AND DISTRIBUTION OF LEUKOCYTES

The most striking differences in cell type and distribution were observed with mast cells and macrophages (see Figure 9.3). In both gaiter and thigh biopsies, mast cell numbers were two to four times greater than control in Class 4 and 5 patients around arterioles and PCVs ($p < 0.05$). Class 6 patients demonstrated no difference in mast cell number compared to controls. Mast cell numbers around capillaries did not differ across groups in either gaiter or thigh biopsies. Macrophages demonstrated increased numbers in Class 5 and 6 patients around arterioles and PCVs, respectively ($p < 0.05$). Differences in macrophage numbers around capillaries were observed primarily in Class 4 patients in both gaiter and thigh biopsies. Surprisingly, lymphocytes, plasma cells, and neutrophils were not present in the immediate perivascular space. Fibroblasts were the most common cells observed in both gaiter and thigh biopsies. It was speculated that mast cells and macrophages may function to regulate tissue remodeling resulting in dermal fibrosis.[40] The mast cell enzyme chymase is a potent activator of matrix metal-

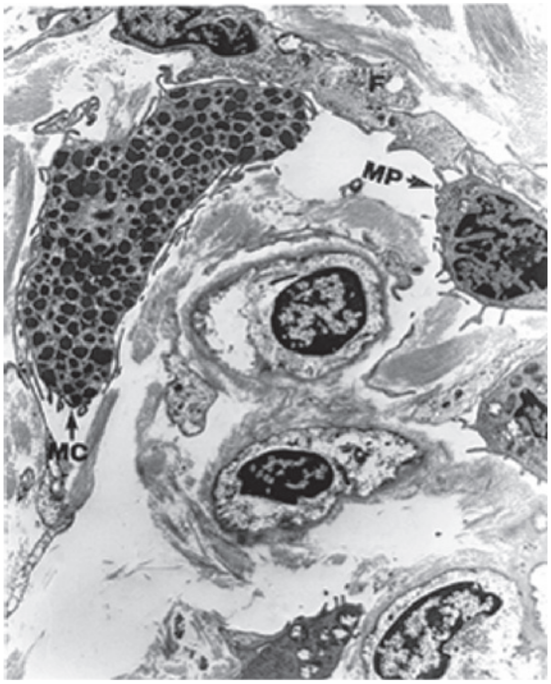

FIGURE 9.3 Electron micrograph (Mag 4300×) of mast cells (MC), macrophages (MP) and fibroblast (F) surrounding a central capillary from dermal biopsy of a patient with CEAP class 4 chronic venous insufficiency.

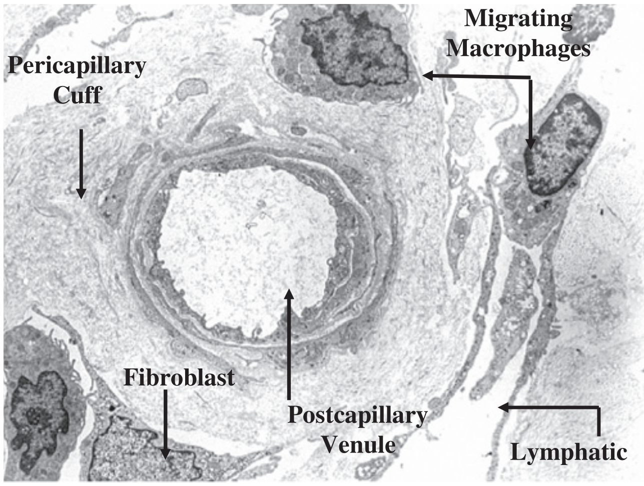

FIGURE 9.4 Electron micrograph (Mag 4300×) of a well-developed perivascular cuff in close proximity to a fibroblast in a patient with CEAP class 6 chronic venous insufficiency. Long arrow points to macrophages that appear to be entering a lymphatic lumen.

loproteinase-1 and -3 (collagenase and stromelysin).[47–49] In an *in vitro* model using the human mast cell line HMC-1, these cells were reported to spontaneously adhere to fibronectin, laminin, and collagen types I and III, all components of the perivascular cuff (see later).[49] Chymase also causes release of latent TGF-β1 secreted by activated endothelial cells, fibroblasts, and platelets from extracellular matrices.[50] Release and activation of TGF-β1 initiate a cascade of events in which macrophages and fibroblasts are recruited to wound healing sites and stimulated to produce fibroblast mitogens and connective tissue proteins, respectively.[51] Mast cell degranulation leading to TGF-β1 activation and macrophage recruitment may explain why decreased mast cell and increased macrophage numbers were observed in Class 6 patients. Macrophage migration, as evidenced by the frequent appearance of cytoplasmic tails in perivascular macrophages, further substantiates the concept of inflammatory cytokine recruitment (see Figure 9.4).

EXTRACELLULAR MATRIX (ECM) ALTERATIONS

Once leukocytes have migrated to the extracellular space they localize around capillaries and postcapillary venules. The perivascular space is surrounded by extracellular matrix (ECM) proteins and forms a perivascular cuff. Adjacent to these perivascular cuffs and throughout the dermal interstitium is an intense and disorganized collagen deposition.[33,40] Perivascular cuffs and the accompanying collagen deposition are the *sine qua non* of the dermal microcirculation in CVI patients (see Figure 9.4). The perivascular cuff originally was thought to be the result of fibrinogen extravasation and erroneously referred to as a fibrin cuff.[5] It is now known that the cuff is a ring of ECM proteins consisting of collagen types I and III, fibronectin, vitronectin, laminin, tenascin, and fibrin.[52] The role of the cuff and its cell of origin is not completely understood. The investigation by Pappas et al. suggested that the endothelial cells of the dermal microcirculation were responsible for cuff formation.[40] The cuff was once thought to be a barrier to oxygen and nutrient diffusion; however, recent evidence suggests that cuff formation is an attempt to maintain vascular architecture in response to increased mechanical load.[53] Although perivascular cuffs may function to preserve microcirculatory architecture, several pathologic processes may be related to cuff formation. Immunohistochemical analyses have demonstrated transforming growth factor-β_1 (TGF-β_1) and $\pm_2$-macroglobulin in the interstices of perivascular cuffs.[54] It has been suggested that these "trapped" molecules are distributed abnormally in the dermis leading to altered tissue remodeling and fibrosis. Cuffs may also serve as a lattice for capillary angiogenesis explaining the capillary tortuosity and increased capillary density observed in the dermis of CVI patients.

PATHOPHYSIOLOGY OF STASIS DERMATITIS AND DERMAL FIBROSIS

The mechanisms modulating leukocyte activation, fibroblast function, and dermal extracellular matrix alterations have been the focus of investigation in the 1990s. CVI is a disease of chronic inflammation due to a persistent and sustained injury secondary to venous hypertension. It is hypothesized that the primary injury is extravasation of macromolecules (i.e., fibrinogen and $\pm_2$-macroglobulin) and red blood cells (RBCs) into the dermal interstitium.[33,34,44,45,54] RBC degradation products and interstitial protein extravasation are potent chemoattractants and presumably represent the initial underlying chronic inflammatory signal responsible for leukocyte recruitment. It has been assumed that these cytochemical events are responsible for the increased expression of ICAM-1 (intercellular adhesion molecule-1) on endothelial cells of microcirculatory exchange vessels observed in CVI dermal biopsies.[39,55] ICAM-1 is the activation-dependent adhesion molecule utilized by macrophages, lymphocytes, and mast cells for diapedesis. As stated earlier, all these cells have been observed by immunohistochemistry and electron microscopy in the interstitium of dermal biopsies.[39,40]

CYTOKINE REGULATION AND TISSUE FIBROSIS

Leukocyte recruitment, ECM alterations, and tissue fibrosis are characteristic of chronic inflammatory diseases caused by alterations in TGF-β_1 gene expression and protein production. To determine the role of TGF-β_1 in CVI, dermal biopsies from normal patients and CEAP class 4, 5, and 6 CVI patients were analyzed for TGF-β_1 gene expression, protein production, and cellular location.[56] Quantitative RT-PCR for TGF-β_1 gene expression was performed on 24 skin biopsies obtained from 24 patients. Patients were separated into four groups according to the ISCVS/SVS classification for CVI: normal skin (n = 6), CEAP class 4 (n = 6), CEAP class 5 (n = 5), and CEAP class 6 (n = 7). TGF-β_1 gene transcripts for controls, Class 4, 5, and 6 patients were 7.02 $\pm$ 7.33, 43.33 $\pm$ 9.0, 16.13 $\pm$ 7.67, and 7.22 $\pm$ 0.56 $\times$ 10^{-14} moles/g total RNA, respectively. The differences in TGF-β_1 gene expression in Class 4 patients was significantly elevated compared to control and Class 5 and 6 patients ($p < 0.05$).[56] An additional 38 patients had 54 biopsies from the lower calf (LC) and lower thigh (LT) analyzed for TGF-β_1 protein concentration. The amounts of active TGF-β_1 in picograms/gram (pg/gm) of tissue from LC and LT biopsies compared to normal skin biopsies were as follows: Normal skin (<1.0 pc/gm), Class 4 (LC, 5061 $\pm$ 1827, LT 317.3 $\pm$ 277), Class 5 (LC, 8327 $\pm$ 3690, LT 193 $\pm$ 164), and Class 6 (LC, 5392 $\pm$ 1800, LT, 117 $\pm$ 61) (see Figure 9.5). Differences between normal skin and Class 4 and 6 patients were significant ($p < 0.05$ and $p < 0.01$, respectively). No differences between Class 4, 5, and 6 patients were observed. Differences between LC and LT within each CVI group were significant (Class 4, $p < 0.003$, Class 5, $p < 0.008$, Class 6, $p < 0.02$). These data demonstrate that in areas of clinically active CVI, increased amounts of active TGF-β_1 are present compared to normal skin. Furthermore, active TGF-β_1 protein concentrations of biopsies from the LT did not differ from normal skin demonstrating a regionalized repsonse to injury.[56]

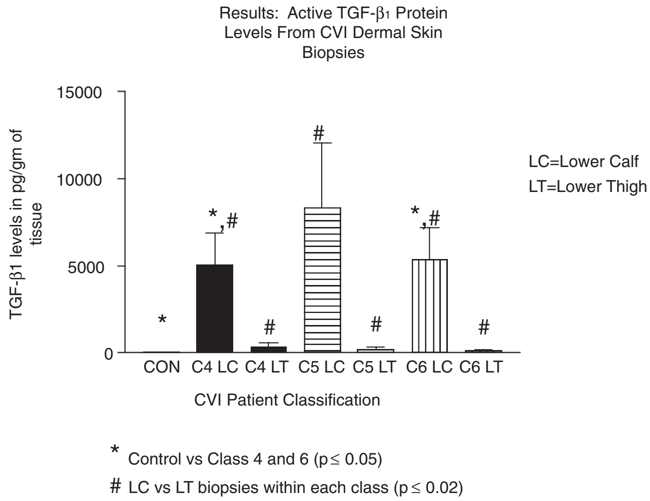

FIGURE 9.5 Active TGF-β1 levels indicating increased levels in class 4, 5, and 6 patients compared to controls and ipsilateral thigh biopsies. Con-Control patients without venous disease, LT-Ipsilateral thigh, LC-Ipsilateral diseased skin.

Immunohistochemistry and immunogold labeling experiments were performed to identify the sources of active TGF-β_1 protein production. Immunohistochemistry of normal skin and ipsilateral thigh biopsies of CVI patients demonstrated mild TGF-β_1 in the basal layer of the epidermis. The dermis demonstrated few capillaries, ordered collagen architecture, and no interstitial leukocytes. CVI dermal biopsies from areas of clinically active disease demonstrated staining of the basal layer of the epidermis, interstitial leukocytes, and fibroblasts. Many perivascular leukocytes demonstrated positive staining of intracellular granules and appeared morphologically similar to previously reported mast cells (see Figures 9.3 and 9.6).[56] Numerous capillaries with perivascular cuffs were observed; however, cuffs did not stain positively for TGF-β_1.[56] This study conflicts with the observations reported by Higley et al. in which they reported positive TGF-β_1 staining in perivascular cuffs and an absence of TGF-β_1 in the provisional matrix of the venous ulcer compared to healing donor skin graft sites.[54] They concluded that TGF-β_1 was therefore abnormally "trapped" in the perivascular cuff and therefore unavailable for normal

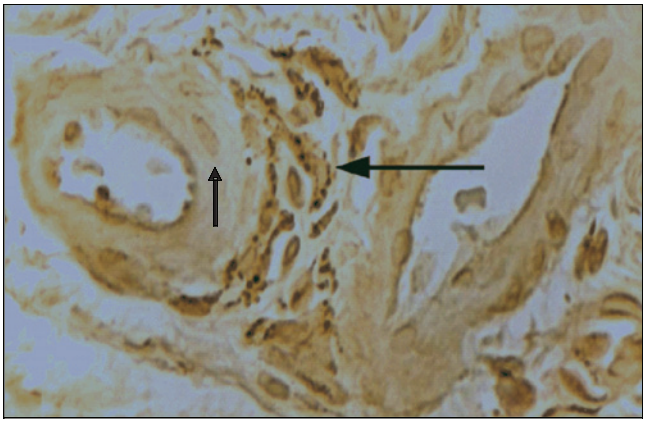

FIGURE 9.6 Immunohistochemistry (Mag 575×) of dermal skin biopsy demonstrating transforming growth factor-β1 positive granules (long arrow) in leukocytes surrounding a perivascular cuff and leukocytes migrating through a perivascular cuff (short arrow).

granulation tissue development. Differences between the two studies may relate to biopsy site selection. Higley et al. biopsied chronic, nonhealing venous ulcer edges and ulcer bases, whereas patients with active ulcers in the study by Pappas et al. were biopsied five to ten centimeters away from an active ulcer. Therefore, the former study reflects the biology of chronic wound healing and our data suggest active tissue remodeling in response to a chronic injury stimulus.

Immunogold labeling confirmed the presence of TGF-β_1 in dermal leukocytes. Positive labeling of gold particles similarly were observed in collagen fibrils of the ECM. This observation may explain why the molecular regulation of TGF-β_1 in CVI patients demonstrates differential gene and protein production according to disease classification. As stated earlier, the gene expression of TGF-β_1 was increased in Class 4 patients only, and the protein production essentially was increased in Class 4, 5, and 6 patients. These differences may be related to disease severity and the pluripotential responses of TGF-β_1. TGF-β_1 can have inhibitory and stimulatory effects that are primarily dependent on local concentration, cell source, and surrounding ECM. In the study by Pappas et al., Class 4 patients were younger than the other study groups, never experienced an episode of venous stasis ulceration, and clinically demonstrated less dermal tissue fibrosis. TGF-β_1 in these patients therefore may be involved in limiting the response to injury. Indeed, one could speculate that early on in the disease process, a low-grade production of TGF-β_1 is a normal wound-healing response and may serve to prevent the onset and development of tissue fibrosis. With continued and prolonged exposure, an imbalance in tissue remodeling in patients with Class 5 and 6 disease clinically manifests itself as dermatofibrosis. A pathologic effect of increased ECM deposition is an alteration in the storage and release of growth factors.[57] The latent form of TGF-β_1 is secreted from cells bound to one of three latent TGF-β_1 binding proteins (LTBP). Once secreted, LTBPs mediate binding of latent TGF-β_1 to matrix proteins. Matrix release of TGF-β_1 is mediated by multiple serine proteinases including plasmin, mast cell chymase, and leukocyte elastase.[50,58–60] An increase in the number of mast cells and circulating leukocyte elastase have been reported previously in CVI patients.[40,61] The increase in active TGF-β_1 observed in Class 5 and 6 patients therefore may result from ECM release of latent TGF-β_1, resulting in tissue fibrosis. This hypothesis is consistent with the demonstration of immunogold labeling to collagen fibrils in the ECM of CVI patients. The modulation of TGF-β_1 release from the ECM may therefore provide a faster means of signal transduction than simple control of gene expression, and therefore may explain the sustained increase of TGF-β_1 in Class 5 and 6 patients in the absence of increased gene expression. This study did not demonstrate increased TGF-β_1 staining in the ECM by ICC because the primary antibody used was specific only for active TGF-β_1 and therefore may have missed LAP and LTBP associated TGF-β_1.

The distribution and location of several other growth factors in the skin of CVI patients have also been investigated. Peschen et al. reported on the role of platelet-derived growth factor receptor alpha and beta (PDGFR-± and -β) and vascular endothelial growth factor (VEGF).[62] Skin biopsies from 30 patients were separated into five groups: Group 1, patients with reticular veins; Group 2, venous eczema; Group 3, skin pigmentation; Group 4, lipodermatosclerosis; and Group 5, patients with active leg ulcers; with a total of six patients in each group. Biopsies were studied with immunohistochemistry and the degree of immunoreactivity assessed with a scoring system by two blinded reviewers. Peschen et al. reported that PDGFR-± and -β and VEGF expression was strongly increased in the stroma of CVI patients with eczema and active ulcers compared to patients with reticular veins and pigmentation changes only.[62] To a lesser degree, patients with lipodermatosclerosis demonstrated immunoreactivity to PDGFR-± and -β and VEGF as well. PDGFR-± and -β expression was elevated considerably in the capillaries and surrounding fibroblasts and inflammatory cells of venous eczema patients. In addition, immunoreactivity was increased in dermal fibroblasts, smooth muscle cells, and vascular cells of lipodermatosclerosis patients compared to patients with reticular veins only. The greatest expression of PDGFR-± and -β was observed in mesenchymal cells and vascular endothelial cells of patients with active venous ulcers. VEGF immunoreactivity correlated with disease severity. VEGF positive capillary endothelial cells and pericapillary cells increased in patients with venous eczema, lipodermatosclerosis, and active venous ulceration, respectively. In a subsequent investigation, these authors reported that with progression of CVI dermal

pathology the endothelial cell adhesion molecules intercelluar and vascular adhesion molecules (ICAM-1, VCAM-1) and their corresponding leukocyte ligands LFA-1 and VLA-4 were upregulated on leukocytes and endothelial cells.[55] Based on these observations, the authors speculated that leukocyte recruitment, capillary proliferation, and interstitial edema in CVI patients may be regulated through PDGF and VEGF by upregulation of adhesion molecules leading to leukocyte recruitment, diapedesis, and release of chemical mediators.[55]

In summary, these investigations indicate that progression of CVI dermal pathology is mediated by a cascade of inflammatory events. Venous hypertension causes extravasation of macromolecules like fibrinogen and red blood cells that act as potent inflammatory mediators. These mediators cause an upregulation of adhesion molecules and the expression of growth factors like PDGF and VEGF, which result in leukocyte recruitment. Monocytes and mast cells travel to the site of injury, which activate or release TGF-β_1 and probably other undiscovered chemicals as well. What effect growth factor binding has on fibroblast and endothelial cell function has been the focus of numerous investigations in the 1990s.

DERMAL FIBROBLAST FUNCTION

Several studies have reported aberrant phenotypic behavior of fibroblasts isolated from venous ulcer edges when compared to fibroblasts obtained from ipsilateral thigh biopsies of normal skin in the same patients. Hasan et al. compared the ability of venous ulcer fibroblasts to produce ±I procollagen mRNA and collagen after stimulation with TGF-β_1.[63] These authors were not able to demonstrate differences in ±I procollagen mRNA levels after stimulation with TGF-β_1 between venous ulcer fibroblasts and normal fibroblasts (control) from ipsilateral thigh biopsies. However, collagen production was increased by 60% in a dose-dependent manner in controls whereas venous ulcer fibroblasts were unresponsive. This unresponsiveness was associated with a four-fold decrease in TGF-β_1 type II receptors. In a follow-up report, Kim et al. indicated that the decrease in TGF-β_1 type II receptors was associated with a decrease in phosphorylation of the TGF-β_1 receptor substrates SMAD 2 and 3 as well as p42/44 mitogen activated protein kinases.[64] A similar investigation reported a decrease in collagen production from venous ulcer fibroblasts and similar amounts of fibronectin production when compared to normal controls.[65]

Fibroblast responsiveness to growth factors was further delineated by Stanley et al.[66] These investigators characterized the proliferative responses of venous ulcer fibroblasts when stimulated with basic fibroblastic growth factor (bFGF), epidermal growth factor (EGF), and interleukin 1-β (IL-1β). In their initial study, they reported that venous ulcer fibroblast growth rates were markedly suppressed when stimulated with bFGF, EGF, and IL-1β. In a follow-up investigation these authors noted that the previously observed growth inhibition could be reversed with bFGF.[67] Lal et al. reported that the proliferative responses of CVI fibroblasts to TGF-β_1 correlated with disease severity.[68] Fibroblasts from patients with CEAP Class 2 and 3 disease retain their agonist-induced proliferative capacity. Class 4 and 5 fibroblasts demonstrated diminished agonist-induced proliferation, whereas Class 6 (venous ulcer fibroblasts) did not proliferate after TGF-β_1 stimulation, confirming the observations made by the previous investigators. Phenotypically, venous ulcer fibroblasts appeared large and polygonal with varied nuclear morphologic features, whereas normal fibroblasts appeared compact and tapered with well-defined nuclear morphologic features. Venous ulcer fibroblasts appeared morphologically similar to fibroblasts undergoing cellular senescence. Therefore, the blunted growth response of CVI venous ulcer fibroblasts appears related to development of cellular senescence.[66,69]

Other characteristics of senescent cells are an overexpression of matrix proteins such as fibronectin (cFN) and enhanced activity of β-galactosidase (SA-β-Gal). In an evaluation of seven patients with venous stasis ulcers, it was noted that a higher percentage of SA-β-Gal positive cells in venous ulcers compared to normal controls (6.3% vs 0.21%, $p < 0.0.6$).[67] It was also reported that venous ulcer fibroblasts produced one to four times more cFN by Western blot analysis compared to controls.[69] These data support the hypothesis that venous ulcer fibroblasts phenotypically behave like senescent cells. However, senescence is probably the end manifestation of a wide spectrum of events that leads to proliferative resistance and cellular dysfunction. Telomeres and telomerase activity are the *sine qua non* of truly senescent cells. To date, there are no reported studies indicating an abnormality in CVI fibroblast telomere or telomerase activity. Absent these investigations, the true role of senescence in CVI remains ill-defined.

ROLE OF MATRIX METALLOPROTEINASES (MMPS) AND THEIR INHIBITORS IN CVI

The signaling event responsible for the development of a venous ulcer and the mechanisms responsible for prolonged wound healing are poorly understood. Wound healing is an orderly process that involves inflammation, re-epithelialization, matrix deposition, and tissue remodeling. Tissue remodeling and matrix deposition are processes controlled by matrix metalloproteinases (MMPs) and tissue inhibitors of matrix metalloproteinases (TIMPs). In general, MMPs and TIMPs are not constitutively expressed. They are induced temporarily in response to exogenous signals such

as various proteases, cytokines or growth factors, cell-matrix interactions, and altered cell-cell contacts. TGF-β_1 is a potent inducer of TIMP-1 and collagen production and inhibitor of MMP-1 through regulation of gene expression and protein synthesis. Several studies have demonstrated that prolonged and continuous TGF-β_1 production causes tissue fibrosis by stimulating ECM production and inhibiting degradation by affecting MMP and TIMP production. Alterations in MMP and TIMP production may similarly modulate the tissue fibrosis of the lower extremity in CVI patients. Several investigators have reported that the gelatinases MMP-2 and -9 as well as TIMP-1 are increased in the exudates of patients with venous ulcers compared to acute wounds.[70–72] However, analyses of biopsy specimens have demonstrated variable results. Herouy et al. reported that MMP-1, and -2 and TIMP-1 are increased in patients with lipodermatosclerosis compared to normal skin.[73] In a subsequent investigation, biopsies from venous ulcer patients were found to have increased levels of the active form of MMP-2 compared to normal skin[74] as well as increased immunoreactivity to EMMPRIN (Extracelluar inducer of MMP), MT1-MMP (Membrane Type 1), and MT2-MMP in the dermis and perivascular regions of venous ulcers.[75] Saito et al. were unable to identify differences in overall MMP-1, -2, and -9 and TIMP-1 protein levels or activity in CVI patients with CEAP Class 2 through 6 disease compared to normal controls or CVI groups.[76] However, within a clinical class, MMP-2 levels were elevated compared to MMP-1, and -9 and TIMP-1 in patients with Class 4 and Class 5 disease. These data indicate that active tissue remodeling is occurring in patients with CVI. Which matrix metalloproteinases are involved and how they're activated and regulated are currently unclear. It appears that MMP-2 may be activated by urokinase plasminogen activator (uPA). Herouy et al. observed increased uPA and uPAR mRNA and protein levels in patients with venous ulcers compared to normal skin.[77] The elevated levels of active TGF-β_1 in the dermis of CVI patients suggests a regulatory role for TGF-β_1 in MMP and TIMP synthesis and activity. However, there is currently no direct evidence indicating such a relationship.

CONCLUSION

The mechanisms regulating varicose vein development and the subsequent dermal skin sequelae caused by chronic ambulatory venous hypertension only recently have been investigated. It is clear that varicose vein formation has a genetic component that is linked to environmental stimuli. Susceptible patients develop vein wall fibrosis and loss of valvular competence that leads to venous hypertension. The transmission of high venous pressures to the dermal microcirculation causes extravasation of macromolecules and red blood cells that serve as the underlying stimulus for inflammatory injury. Activation of the microcirculation results in cytokine and growth factor release leading to leukocyte migration into the interstitium. At the site of injury, a host of inflammatory events is set into action. TGF-β_1 appears to be a primary regulator of CVI induced injury. TGF-β_1 secretion from leukocytes with subsequent binding to dermal fibroblasts is associated with intense dermal fibrosis and tissue remodeling. In addition, decreased TGF-β_1 type II receptors on venous ulcer fibroblasts are associated with diminished fibroblast proliferation. Fibroblast proliferation diminishes with disease progression ultimately leading to senescence and poor ulcer healing. In addition, increases in MMP-2 synthesis appear to increase tissue remodeling and further impede ulcer healing. As our understanding of the underlying cellular and molecular mechanisms that regulate CVI and ulcer formation increase, therapeutic interventions for treatment and prevention will ultimately follow.

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CHAPTER

10

Mechanism and Effects of Compression Therapy

HUGO PARTSCH

Compression therapy is a very effective treatment modality whose mechanisms are not yet fully understood.

The clinical effects depend mainly on two factors, interface pressure and stiffness.

Interface pressure is the pressure exerted by a compression device on a specific skin area. Stiffness is defined by the increase of the interface pressure induced by the increase of the circumference of a limb segment when muscles are contracting.[1]

INTERFACE PRESSURE

Compression Hosiery

The pressure ranges given for compression hosiery are measured in the laboratories of the producers by determining the force that is necessary to stretch the ankle part of the stocking in transverse direction. The pressure values are calculated from the force-extension diagram of the elastic fabric, the so-called hysteresis curve, projected to a leg model with defined circular cross sections using Laplace's law. This formula describes the relationship between the interface pressure P, which is directly proportional to the tension (T) of the bandage and inversely proportional to the radius (R) of the curvature to which it is applied ($P = T/R$). The proportion of stretch and force, which corresponds to the steepness of the so-called slope in the hysteresis curve, reflects the elasticity of the material of the stocking.

Several industrial measuring systems for obtaining hysteresis curves are used, such as the Hosy method, the Hatra tester, the Instron method, the French ITF method, and others.[2]

Table 10.1 gives a comparison of compression classes for ready-to-wear and custom stockings used in several countries. The range of compression pressures and the description of these classes vary among different countries. Therefore, it is recommended to use the pressure range in mm Hg rather than compression classes for a better universal understanding. However, comparisons may also be problematic since the given ranges are measured by different methods. These facts underline the necessity of *in vivo* pressure measurements on the individual leg, at least in future clinical studies.

The unit for pressure is 1 Pascal (Pa), which is 1 Newton (N) per square meter. In the medical field, for example, measuring blood pressure, the usual unit for pressure is the weight of one cubic millimeter of mercury.

The pressure values in Table 10.1 refer to the ankle region, called the *level B*. Proximal measuring points on the leg are:[1]

- B1, the point at which the Achilles tendon changes into the calf muscle
- C, corresponding to the calf at its maximum girth
- D, just below the tibial tuberosity
- E, over the patella
- F, between K and E
- G, 5 cm below K in the upright position
- H, at the greatest lateral trochanteric projections of the buttock
- K, at the center point of the crutch

As the circumference of the leg progressively increases, a compression gradient is produced, which is defined by the European prestandard as follows: for level B1, 70–100%; for C and D, 50–80%; and for F or G, 20–40% for compression class III and IV; 20–60% for the classes A–I; and 20–50% for class II.

TABLE 10.1 Compression Classes Used in Several Countries (Values are mm Hg, 1 mm Hg = 1,333 hPa)

Compression class	EU (CEN)[64]	USA	UK (BS 6612)[65]	France	Germany[66]
A	10–14 (light)				
I	15–21 (mild)	15–20 (moderate)	14–17 (light)	10–15	18–21 (light)
II	23–32 (moderate)	20–30 (firm)	18–24 (medium)	15–20	23–32 (medium)
III	34–46 (strong)	30–40 (extra firm)	25–35 (strong)	20–36	34–46 (strong)
IV	>49 (very strong)	40+		>36	>49 (very strong)

The values indicate the compression exerted by the hosiery at a hypothetical cylindrical ankle

TABLE 10.2 Compression Materials

Elastic, long-stretch material	Inelastic, short-stretch material	Nonstretch material
Compression stockings	Short-stretch bandages	Zinc paste bandages, Unna boot
Long-stretch bandages	Multilayer short-stretch bandages*	Velcro band devices
Extensibilty >100%	Extensibility <100%*	Extensibility 0–10%
Low stiffness	Medium stiffness	High stiffness
Exerts pressure when applied with stretch	Pressure increases when movement causes calf muscle to contract	Pressure increases when movement causes calf muscle to contract

*Bandages consisting of several elastic components with an extensibility of the single layer >100%, for example as the “four-layer bandage,” will become relatively inelastic when applied in more layers and therefore may also be ranged into this category.

Compression Bandages

The interface pressure of compression bandages depends on the experience and the skill of the bandager and only rarely is declared. For future trials it will be essential to measure the interface pressure as a parameter characterizing the “dosage” and hence the efficacy of the bandage.

Several devices for measuring the interface pressure on the individual leg have been described.[2] The pressure measured under static (resting) conditions is termed *resting pressure*; that measured on the moving patient is known as *working pressure*.

When pressure data are reported it is essential to indicate the type and size of the transducer and the exact localization on the extremity.[3]

The ankle region, which is a reference point for stocking manufacturers (B-segment), is not a suitable location for reliable *in vivo* measurement because of the radius changes varying widely due to the bony prominences and tendons prevailing in this segment. This is the reason why some reports of stocking pressures have given lower values from B than from the more proximal segment B1.

STIFFNESS

It has been shown that compression devices exerting the same resting pressure have different hemodynamic effects on venous reflux and venous pumping function depending on the elastic property of the material.[4] This can be characterized by the stiffness, which plays an important role concerning the performance of a compression device during standing and walking, and which can be measured in vivo.

Stiffness is defined by the increase of compression per centimeter increase in the circumference of the leg, expressed in hectopascals per centimeter and/or millimeters of mercury per centimeter.[1] A very appropriate method to measure a dynamic stiffness index during walking has been described by a Dutch group.[5] However, this technique requires sophisticated instrumentation and can be performed only in specialized laboratories.

We have proposed a very simple method that is able to differentiate inelastic from elastic material by measuring the difference between the standing pressure and the supine pressure at the B1 region, which is the area where the tendinous part of the medial gastrocnemius muscle changes into the muscular part.[6] The standing position is considered to be a snap-shot of the walking cycle. Therefore pressure sensors also may be used that are not able to register continuous pressure changes.

Especially when several textiles are combined in a multilayer bandage, the stiffness of the final bandage will increase because of the friction of the layers.[2] The same is true when two compression stockings are donned over each other.

Compared with *in vitro* measurements stiffness corresponds to the slope of the hysteresis curve *in vitro*.

COMPRESSION MATERIAL

Based on the principles mentioned earlier, several textiles used for compression therapy can be differentiated (see Table 10.2).

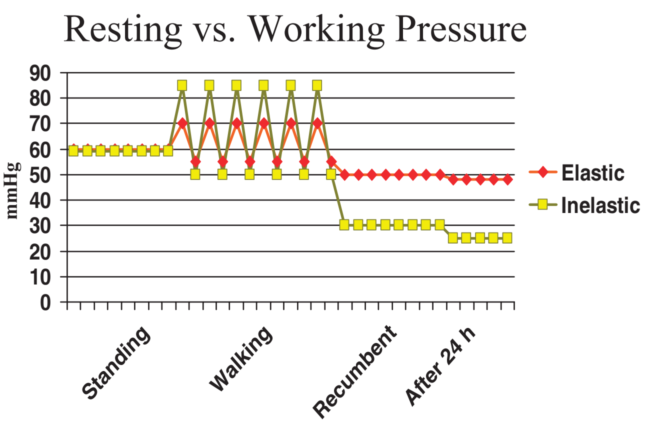

FIGURE 10.1 Interface pressure measured on the medial aspect of the leg (B1) of an elastic and an inelastic bandage. Both bandages are firmly applied and exert a pressure of 60 mm Hg immediately after application in the standing position. During walking much higher pressure peaks are obtained with inelastic than with elastic material. When the patient lies down and also after 24 hours, elastic bandages show only a mild reduction of pressure. The more intense pressure loss of the inelastic material is the reason why these bandages also are tolerated during nighttime, and why they should be renewed when getting too loose.

PERFORMANCE OF COMPRESSION MATERIALS

Elastic textiles exert pressure by being stretched. During walking only small pressure peaks will occur since the elastic material gives way with every step. The working pressure is therefore not much higher than the resting pressure (see Figure 10.1). Due to the retraction of the elastic fibers there is only a small reduction of interface pressure in the sitting and lying position. A continuous high resting pressure may cause unpleasant feelings during rest and is strictly contraindicated in patients with arterial occlusive disease. Therefore elastic bandages and firm medical compression stockings should be removed over nighttime. The main advantage of elastic material is that it can also be handled by nonexperienced staff and even by the patients themselves.

Short-stretch material and completely rigid devices show a high working pressure with high peaks during walking that are able to occlude leg veins intermittently, thereby reducing ambulatory venous hypertension.[7,14]

During walking, nonyielding material will exert similar effects as intermittent pneumatic compression, especially concerning the release of anti-inflammatory, anticoagulatory, and vasoactive mediators from the endothelial cells.[8] These effects are probably the reason for the fact that the best healing rates of venous ulcers have been described with multilayer high-pressure bandages.[9] A considerable fall of pressure will occur when the patient lies down, so that short-stretch bandages may better be tolerated in the resting position. The pressure loss of up to 40% in the first two hours is caused by an immediate reduction of the limb volume and should be taken into account by applying an inelastic bandage with a much higher strength than an elastic bandage, which needs some experience. Due to the pressure fall, inelastic bandages are well tolerated also during nighttime. In patients with massive edema they should be reapplied after short periods of time in the initial phase when they get loose. Later on they may be worn for one week and longer. In the presence of arterial occlusions inelastic bandages should be applied with a very low resting pressure, which should be adjusted to the systolic ankle pressure in order not to interfere with the reduced arterial inflow. During movement there will be a massage of the limb, which may be compared with intermittent pneumatic compression. Bandages applied with several elastic layers get similar elastic properties as short-stretch bandages.

Intermittent pneumatic compression offers adjunctive beneficial effects, especially in patients with a restricted walking ability. In addition to the decongestive effect, an increase of arterial flow and a release of vasoactive and anticoagulatory mediators from the endothelial cells have been documented during the last few years.[8,10]

Therapy Phase and Maintenance Phase of Compression Therapy

In general, we prefer multilayer short-stretch or completely nonelastic material for the therapy phase of severe stages of chronic venous insufficiency like venous ulcers, for lymphedema, and also for acute phlebitis and deep vein thrombosis.[11] When the leg ulcers are healed and when the extremity is fairly free from edema, elastic material, preferably compression stockings, is used in order to maintain this condition (maintenance phase).

PHYSIOLOGICAL EFFECTS OF COMPRESSION THERAPY

Some physiological effects of compression therapy as documented in several studies are summarized in Table 10.3.[1,12]

The application of continuous compression is contraindicated in patients with advanced peripheral arterial disease or severe sensory impairment.

Several effects of compression therapy have been demonstrated in the acute experiment using intermittent pneumatic compression. It may be assumed that similar effects will also occur during walking with inelastic bandages.

TABLE 10.3 Effects of Compression Therapy (Stockings and Bandages)

Parameters	Effect
Tissue pressure	Increase
Edema	Decrease
Venous volume	Decrease
Venous velocity	Increase
Blood shift into central compartments	Increase
Venous refluxes	Decrease
Venous pump	Improvement
Arterial flow	Increase (intermittent compression)
Microcirculation	Improvement
Lymph drainage	Improvement

Tissue Pressure and Edema

By increasing the tissue pressure compression works against filtration, which is the most important mechanism to prevent or to remove edema. Occupational leg swelling in sitting and standing professions can be prevented by light compression stockings, which are also able to reduce mild edema.[13] Reduction in intradermal edema can be measured with ultrasound in patients with CVI and lipodermatosclerosis. Severe stages of limb swelling benefit more from inelastic compression devices exerting higher pressure.

Compression may reveal beneficial effects also in nonphlebological causes of edema like inflammatory edema (arthritis, cellulitis), cardiac, dysproteinemic, renal edema, lymphedema, and cyclic idiopathic edema.[2]

Venous Volume and Venous Blood Flow Velocity

Depending on the exerted pressure and the body position, external compression is able to narrow or to occlude superficial and deep leg veins.[14]

In the supine position an external pressure of 10–15 mm Hg is enough to decrease the venous diameter. The resulting increase of blood flow velocity as clearly shown by measuring the circulation time with isotopes[15] is the rationale for recommending light compression stockings for thromboprophylaxis in bedridden patients.

Venous volume can be assessed using air-plethysmography (APG) that shows a significantly more pronounced reduction by inelastic than by elastic compression, even when the resting pressure is the same.[4]

In the upright position elastic stockings will have only a minor effect on decreasing the diameter of the leg veins.[16] However, a very small decrease of venous diameter will result in an overproportional decrease of the local blood volume as demonstrated by several plethysmographic studies.[4,12]

Blood Shift into Central Compartments

Firm compression bandages applied on both lower extremities may redistribute blood toward the central parts of the body. This can lead to an increase of the preload of the heart by about 5% and should be avoided in patients with borderline cardiac function.[17]

Decrease of Venous Refluxes and Improvement of the Venous Pump

Using APG in patients with deep venous incompetence, it could be shown that compression with increasing interface pressure was associated with a decreasing amount of total reflux measured by venous filling index.

A statistically significant reduction of refluxes was achieved with pressures over 30 mm Hg for inelastic and over 40 mm Hg for elastic material.[4]

The reduction of venous refluxes in patients with chronic venous insufficiency by external compression explains the improvement of the venous pumping function. Plethysmographic studies have shown an increasing improvement of the venous pump with increasing stocking pressures, starting with an ankle pressure of around 20 mm Hg.[7,20]

Higher compression pressure using stiff material leads to short phases of intermittent occlusion of the deep veins with every step during muscle contraction. Such intermittent occlusions of deep veins on the leg can be visualized by Duplex.[14] By encasing the veins in a rigid envelope ambulatory venous hypertension may thereby be reduced in patients with deep venous incompetence.[7] Similarly, a progressively increasing pressure on the thigh by using a blood pressure cuff blown up to 40–80 mm Hg led to a progressively decreasing vein diameter and to an abolishment of reflux when the femoral vein segment contained incompetent valves.[18] Reduction of venous refluxes and improvement of ambulatory venous hypertension by external cuff compression could be demonstrated even in patients without any valves (avalvulia). This effect therefore cannot be explained by the common explanation of a coaptation of distended valve leaflets, but seems rather to be due to the intermittent occlusion of the incompetent vein during walking.[19]

Conflicting results have been reported concerning an improvement of ambulatory venous hypertension by compression stockings.[2,7] This may be explained by the fact that the pressure exerted by stockings is too low in order to sufficiently compress the veins in the leg in the upright position. In addition, the elastic material gives way with every step,

whereas inelastic, short-stretch bandages with a double as high resting pressure are able to achieve intermittently short venous occlusions during muscle systole while walking. In patients with severe stages of chronic venous insufficiency a higher compression pressure is needed to improve the disturbed venous pumping function, whereas lower pressure is sufficient in simple varicose veins.[20]

The key mechanism of compression therapy to reduce ambulatory venous hypertension in patients with severe chronic venous insufficiency is an intermittent occlusion of the veins during walking.

In contrast, continuous obliteration of veins by external compression may be desirable after varicose vein surgery in order to stop bleeding and after sclerotherapy to prevent refilling of blood.

To achieve complete venous occlusion the external pressure has to be higher than the intravenous pressure, depending on the body position. It could be demonstrated that an occlusion of the leg veins can be obtained with an external pressure in the range of 20 mm Hg in the supine position, but that in the sitting and standing positions the pressure has to be between 50 and 70 mm Hg.[14] With compression stockings such pressure ranges can be achieved only when rolls or pads are applied over the vein. According to the law of Laplace this will increase the local pressure due to the reduction of the local radius.

Arterial Flow and Microcirculation

A reduction of arterial flow will occur when the external compression pressure exceeds the intra-arterial pressure. This may happen in patients with arterial occlusive disease with a reduced peripheral arterial pressure. In order to avoid ischemic skin lesions from external compression it is therefore essential to measure the peripheral arterial pressure by a Doppler probe before strong compression bandages or stockings are applied. It is generally accepted that a Doppler ankle-brachial index (ABI) of less than 0.5 is a contraindication for compression therapy. However, external compression does not invariably mean reduction of arterial flow. H.N. Mayrovitz reported on several experiments concerning arterial blood flow and compression and was able to demonstrate an increase of the pulsatile flow below the knee in healthy volunteers using nuclear magnetic resonance flowmetry.[21]

Patients with edematous legs and with an ABI between 0.5 and 0.8 may benefit from inelastic or short-stretch bandages applied with a mild resting pressure due to the edema removing massage effect that will occur with every ankle movement. Completely inelastic bandages together with walking have a similar effect as intermittent pneumatic compression. The rhythmic pressure peaks of an inelastic bandage during walking can be compared with those exerted by an intermittent pneumatic pressure pump. Several experiments with intermittent pneumatic compression have demonstrated an increase of arterial flow in patients with arterial occlusive disease.[22] The deciding mechanisms of action are the reduction of edema, an increase of the arteriovenous pressure gradient, myogenic mechanisms, and the release of vasoactive substances from the endothelial cells.

Compression accelerates blood flow in the enlarged capillary loops and reduces capillary filtration due to enhanced tissue pressure. Blood flow and partial oxygen tension in the skin increase and the endothelial adhesion of leukocytes is normalized. Different studies using electron microscopy were able to show a restoration of the structural changes in the media myocytes in stripped veins and a tightening of intercellular junctions. Increasing flow velocity demonstrated by laser Doppler fluxmetry may reduce the likelihood of white blood cells interacting or sticking to endothelium with release of various factors.[23] Effects on mediators involved in the local inflammatory response may explain both the immediate pain relief that occurs with good compression, and ulcer healing.[2,9]

Model experiments with intermittent pneumatic compression were able to demonstrate that there is an increased release of fibrinolytic mediators and of the endothelial relaxing factor (EDRF) nitrogen oxide from the endothelial cells depending on the amount of shear stress produced by the compression waves.[8]

Lymph Drainage

Several beneficial mechanisms of compression therapy on the swollen extremity may be explained by its effects on the lymphatic system:[24]

- Reduction of capillary filtration
- Increase of capillary reabsorption
- Shift of fluid into noncompressed parts of the body
- Increase of lymphatic reabsorption and lymphatic transport
- Breakdown of fibrosclerotic tissue
- Down-regulation of pro-inflammatory cytokines and receptors for growth factors.

External compression increases the interstitial pressure and prevents fluid from filtering out of the capillary network. The amount of the lymphatic load thereby is decreased.

Compression removes more water than protein from the tissue, thereby increasing oncotic tissue pressure and reinforcing the need for sustained compression. Therefore in chronic edema, success is dependent on continued compression.

Compression together with movement enhances the contraction of the lymphangion.

TABLE 10.4 RCTs and Systematic Reviews on Compression Therapy
First column: Indications, following the CEAP classification; second column: number of RCTs identified; columns 3–7: levels of recommendation A, B, C (see later) for bandages (column 3) or different stockings with their pressure ranges (columns 4–7)

Indication	Ref #	Bandage	Stocking 10–14	Stocking 15–21	Stocking 23–32	Stocking 34–46
C0S, C1S	3		B	B		
C1 Sclerother.	2				B	B
C2A	1				C	
C2S	1					C
C2 Pregnancy	1			B	B	
C2 Surgery	7	C	C		C	C
C2 Sclerother	3	C		C		C
C3	1				B	
C4b (LDS)	1				B	
C5	Multiple			B	B	B
C6	Multiple	**A**			B	
DVT Prevention	Multiple		A–B	A–B		
Flight	2		B	B		
DVT Therapy	3	B		B		
PTS Prevention	3				**A**	**A**
Lymphedema	5	B			C	C

Levels of Recommendation:
A: Large RCTs, metaanalysis of homogenous results
B: Only one or smaller RCTs
C: Observational studies, consensus among participants of the consensus meeting

It has been demonstrated that both compression bandaging and exercise stimulated the movement of stagnating lymph through the lymph collector in lymphedema patients, in which the lymphatic trunks are filled. This is probably one explanation for the reduction of intralymphatic hypertension by complex decongestive therapy.

Intermittent pneumatic compression enhances prefascial lymph drainage. Unna boots are able to increase subfascial lymph transport, which is reduced in postthrombotic syndrome.

Consequent compression leads to a morphological improvement of pathological initial lymphatics in patients with lipodermatosclerosis, which can be demonstrated by indirect x-ray lymphography.

CLINICAL EFFECTS OF COMPRESSION THERAPY

The use of compression therapy in various clinical indications is based mainly on experience.

Only a few randomized controlled trials (RCTs) are available that prove the efficacy of compression treatment on the level of evidence-based medicine.[25]

Table 10.4 summarizes the outcome of an international consensus meeting in which all RCTs and systematic reviews have been scored.

Up to now there are only three areas for which evidence-based medicine data show clear clinical benefits of compression therapy: active venous ulceration, prevention of postthrombotic syndrome after deep vein thrombosis, and prevention of thromboembolic events after surgery when combined with anticoagulatory prophylaxis.

In venous ulcers several RCTs have shown that compression is better than no compression and that high pressure is more effective than low pressure. Conflicting results are coming from studies comparing different compression materials, mainly due to the fact that frequently, good bandages have been compared with poor bandages applied by inadequately trained staff. This underlines the need to measure pressure and stiffness of the compression products in future trials.

Compression stockings after proximal deep vein thrombosis (DVT) are able to reduce the incidence of a postthrombotic syndrome some years after the acute event to one half. Immediate mobilization of mobile patients with DVT using compression has been shown not only to reduce pain and swelling in the acute stage but also to achieve less postthrombotic changes after some years.

The overview given in Table 10.4 does not mean that compression is less or not effective in areas with recommendation levels B and C, but that we need more trials in order to improve the scientific evidence for compression devices in the future.

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C H A P T E R

11

Classifying Venous Disease

BO EKLÖF

The Swedish physician and scientist Carl von Linné published a classification of plants based on the number of stamina and pistils in 1735 in *Systema Naturae*. Today, classification of diseases is a basic instrument for uniform diagnosis and meaningful communication about the disease. In chronic venous disorders (CVD) reliance for too long has been placed on the clinical appearance of the superficial effects of CVD, such as spider veins, varicose veins, swelling, skin changes, and ulcerations, without requiring accurate objective testing of the venous system to substantiate the diagnosis. This practice has caused errors of diagnosis and has been largely responsible for the poor correlation of results between treatment methods. There have been several classifications in the past that have added to our understanding of CVD, but all lack the completeness and objectivity needed for scientific accuracy.

PREVIOUS CLASSIFICATIONS OF CVD

The most commonly used classification, particularly in Europe, was Widmer's classification from 1978[1] of chronic venous insufficiency:

Stage I: Edema and dilated subcutaneous veins with corona phlebectatica
Stage II: Trophic lesions of the skin with hyper- or depigmented areas
Stage III: Healed or active ulcer

The criticism against this clinical classification was the nonspecificity of Stage I, and the absence of differentiation between trophic changes in Stage II.

In 1979[2] Hach suggested a grading of great saphenous vein (GSV) incompetence:

Grade I: Reflux in the groin
Grade II: Reflux to above the knee
Grade III: Reflux to just below the knee
Grade IV: Total reflux to the ankle

Hach's thesis was that in severe reflux of the GSV, a viscious internal circle developed because of the large venous blood volume with dilatation of the popliteal and femoral veins leading to deep venous incompetence if the GSV incompetence was not treated.

In 1980,[3] Partsch asked whether in patients with CVD, you could achieve further improvement from other means after compression therapy. Could surgery or sclerotherapy be helpful? He recommended a classification based on involvement of superficial, perforator, and deep veins using objective measures such as foot volumetry and ambulatory venous pressure to discriminate between "betterable" (*besserbare*) and "not betterable" (*nicht besserbare*) patients.

In 1985,[4] Sytchev published a classification very similar to the present CEAP classification, as follows.

Clinical classes

Stages of regional circulatory-trophic disorders:

- Compensation
- Decompensation (cyanosis, edema, cruralgia, or leg pain)

Degrees:

- By the end of the day
- By midday
- At the beginning of the day

Phases:

- Functional trophic disorders (hyper-, hypo-, and anhidrosis of the skin)

- Preulcer condition of tissues
- Trophic ulcers

Etiology

- Primary venous dilatation
- Secondary (postthrombotic) occlusion and recanalization
- Congenital dysplasias

Central hemodynamics

- Compensation
- Decompensation
  — Underloaded
  — Overloaded

The same year,[5] Pierchalla and Tronnier suggested differentiation between primary and secondary (postthrombotic) disease, and between superficial, perforator, and deep venous disease using objective measures.

In 1988,[6] Porter et al. published reporting standards for venous disease developed by an ad hoc committee for the Society for Vascular Surgery (SVS) and the North American chapter of the International Society for Cardiovascular Surgery (ISCVS). This was similar to and based on the Widmer classification with the addition of etiology and anatomic distribution. This was the stimulus for the CEAP classification that followed later.

In 1991,[7] Cornu-Thénard et al. published a clinical classification of the severity of varicose veins by inspection and palpation and calculated the sum of maximum diameter at 7 sites of the leg.

In 1992,[8] Enrici and Caldevilla published a clinical classification on the evolution of the postthrombotic syndrome:

Stage 1: Early postthrombotic syndrome with painful swelling of the leg with distal venous hypertension and venographically demonstrating residual obstruction of the deep veins with competent perforators
Stage 2: Compensatory hypertrophy of the musculo-venous calf muscle pump
Stage 3: Stage 2 plus appearance of secondary varicose veins

Venography shows recanalization with varying reflux with incompetent perforators;

Stage 4: Advanced chronic venous insufficiency with development of a vicious venous recirculation with lipodermatosclerosis and ulceration due to venous hypertension
Stage 5: Phlebo-arthrotic syndrome with immobilization of the ankle

Leads to atrophy of the calf muscle with large circumferential ulcers

Stage 6: Secondary, postthrombotic lymphedema

In 1993,[9] Miranda et al. published a clinical classification:

Stage I: Dilatation of GSV 7 mm by duplex scanning
Stage II: Dilatation of GSV>7 mm without skin changes
Stage III: Stage II plus skin changes
Stage IV: Stage III plus active or healed ulcer

THE CREATION OF THE CEAP CLASSIFICATION

At the fifth annual meeting of the American Venous Forum (AVF) in 1993, John Porter suggested using the same approach as TNM for cancer to develop a classification system for venous diseases. Following a year of intense discussions a consensus conference was held at the sixth annual meeting of AVF in February 1994 on the island of Maui, Hawaii, at which an international *ad hoc* committee, chaired by Andrew Nicolaides, and with representatives from Australia, Europe, as well as the United States, developed the first CEAP consensus document.[10] It contained two parts, a classification of CVD and a scoring system of the severity of CVD. The classification was based on clinical manifestations (C), etiologic factors (E), anatomic distribution of disease (A), and the underlying pathophysiologic findings (P), thus the name CEAP. The severity scoring system was based on three elements: the number of anatomic segments affected, grading of symptoms and signs, and disability. The CEAP consensus statement was published in 26 journals and books in nine languages, truly a universal document for CVD. It was endorsed by the Joint Councils of the SVS and the North American Chapter of the ISCVS, and its basic elements were incorporated into venous reporting standards.[11] Today most published clinical papers on CVD use all or portions of the CEAP classification.

REVISION OF CEAP

Diagnosis and treatment of CVD were developed rapidly in the 1990s and the need for an update of the classification logically followed. Now, it is important to stress that CEAP is a descriptive classification. Venous Severity Scoring (VSS)[12] was developed to allow longitudinal outcomes assessment, but it became apparent that CEAP itself required updating and modification. In April 2002, an *ad hoc* committee on CEAP was appointed by AVF to review the classification and make recommendations for change by 2004, 10 years after its introduction (see Table 11.1). An International *ad hoc* committee also was established to assure continued universal utilization (see Table 11.2). The two committees held four joint meetings in Hawaii, November

TABLE 11.1 Members of the American Venous Forum *ad hoc* Committee on Revision of CEAP classification

Bo Eklof, chair
John Bergan
Peter Gloviczki
Robert Kistner
Mark Meissner, secretary
Gregory Moneta
Frank Padberg
Robert Rutherford
Thomas Wakefield

TABLE 11.2 The International *ad hoc* Committee on Revision of CEAP Classification

The AVF *ad hoc* committee* plus:
Claudio Allegra, It
Pier Luigi Antignani, It
Patrick Carpentier, Fr*
Philip Coleridge Smith, UK*
André Cornu-Thenard, Fr
Ermenegildo Enrici, Ar
Jean Jerome Guex, Fr
Shunichi Hoshino, Jp
Arkadiusz Jawien, Pl
Nicos Labropoulos, USA
Fedor Lurie, USA
Mark Malouf, Au
Nick Morrison, USA
Kenneth Myers, Au*
Peter Neglén, USA
Andrew Nicolaides, Cy
Tomo Ogawa, Jp
Hugo Partsch, At
Michel Perrin, Fr*
Eberhard Rabe, Ge
Seshadri Raju, USA
Vaughan Ruckley, UK*
Ulrich Schultz-Ehrenburg, Ge
Jean Francois Uhl, Fr
Martin Veller, SA
Yuqi Wang, Ch
Zhong Gao Wang, Ch

*Editorial committee

2002; Cancun, Mexico, February 2003; San Diego, August 2003; and Orlando, February 2004.

The following passages summarize the results of these deliberations, by describing the new aspects of the revised CEAP.[13]

The recommended changes, detailed next, include additions to or refinements of several definitions used in describing CVD, refinement of the C-classes of CEAP, addition of the descriptor *n* (no venous abnormality identified), incorporation of the date of classification and level of clinical investigation, and the description of basic CEAP, introduced as a simpler alternative to the full (advanced) CEAP classification.

TERMINOLOGY AND NEW DEFINITIONS

The CEAP classification deals with all forms of chronic venous disorders. The term *chronic venous disorder* (CVD) includes the full spectrum of morphological and functional abnormalities of the venous system from telangiectasias to venous ulcers. Some of these, like telangiectasias, are highly prevalent in the normal adult population, and in many cases the use of the term "disease" is not appropriate. The term chronic venous insufficiency (CVI) implies a functional abnormality of the venous system and usually is reserved for patients with more advanced disease including those with edema (C3), skin changes (C4), or venous ulcers (C5–6).

It was agreed to maintain the overall structure of the CEAP classification, but to add more precise definitions. The following recommended definitions apply to the clinical C classes in CEAP:

Telangiectasia: A confluence of dilated intradermal venules of less than 1 mm in caliber. Synonyms include spider veins, hyphen webs, and thread veins.

Reticular veins: Dilated bluish subdermal veins usually from 1 mm in diameter to less than 3 mm in diameter. They usually are tortuous. This excludes normal visible veins in people with thin, transparent skin. Synonyms include blue veins, subdermal varices, and venulectasies.

Varicose veins: Subcutaneous dilated veins equal to or more than 3 mm in diameter measured in the upright position. These may involve saphenous veins, saphenous tributaries, or nonsaphenous superficial leg veins. Varicose veins usually are tortuous, but tubular saphenous veins with demonstrated reflux may be classified as varicose veins. Synonyms include varix, varices, and varicosities.

Corona phlebectatica: A fan-shaped pattern of numerous small intradermal veins on the medial or lateral aspects of the ankle and foot. This commonly is thought to be an early sign of advanced venous disease. Synonyms include malleolar flare and ankle flare.

Edema: A perceptible increase in volume of fluid in the skin and subcutaneous tissue characteristically indenting with pressure. Venous edema usually occurs in the ankle region, but it may extend to the leg and foot.

Pigmentation: A brownish darkening of the skin resulting from extravasated blood, which usually occurs in the ankle region but may extend to the leg and foot.

Eczema: An erythematous dermatitis, which may progress to a blistering, weeping, or scaling eruption of the skin of the leg. It is most often located near varicose veins but

may be located anywhere in the leg. Eczema usually is seen in uncontrolled CVD but may reflect sensitization to local therapy.

Lipodermatosclerosis (LDS): Localized chronic inflammation and fibrosis of the skin and subcutaneous tissues of the lower leg, sometimes associated with scarring or contracture of the Achilles tendon. LDS is sometimes preceded by diffuse inflammatory edema of the skin, which may be painful and which is often referred to as *hypodermitis*. This condition must be distinguished from lymphangitis, erysipelas, or cellulitis by their characteristically different local signs and systemic features. LDS is a sign of severe chronic venous disease.

Atrophie blanche or white atrophy: Localized, often circular whitish and atrophic skin areas surrounded by dilated capillaries and sometimes hyperpigmentation. This finding is a sign of severe chronic venous disease and not to be confused with healed ulcer scars. Scars of healed ulceration also may have atrophic skin with pigmentary changes but are distinguishable by history of ulceration and appearance from *atrophie blanche* and are excluded from this definition.

Venous ulcer: Full thickness defect of the skin most frequently in the ankle region that fails to heal spontaneously and is sustained by CVD.

REFINEMENT OF C-CLASSES IN CEAP

The essential change here is the division of class C 4 into two subgroups that reflect different severity of disease, and carry a different prognosis in terms of risk of ulceration:

C0: No visible or palpable signs of venous disease
C1: Telangiectasies or reticular veins
C2: Varicose veins—distinguished from reticular veins by a diameter of 3 mm or more
C3: Edema
C4: Changes in the skin and subcutaneous tissue secondary to CVD (now divided into two subclasses to better define the differing severity of venous disease):
C4a: Pigmentation and/or eczema
C4b: Lipodermatosclerosis and/or atrophie blanche
C5: Healed venous ulcer
C6: Active venous ulcer

Each clinical class is further characterized by a subscript for the presence of symptoms (S, symptomatic) or absence of symptoms (A, asymptomatic), for example, $C2_A$ or $C5_S$. Symptoms include aching, pain, tightness, skin irritation, heaviness, and muscle cramps, as well as other complaints attributable to venous dysfunction.

REFINEMENT OF E, A, AND P IN CEAP

To improve the assignment of designations under E, A, and P, a new descriptor *n* is now recommended for use where no venous abnormality is identified. This *n* could be added to E (E*n*: no venous etiology identified), A (A*n*: no venous location identified), and P (P*n*: no venous pathophysiology identified). Observer variability in assigning designations in the past may have been contributed to by the lack of a normal option. Further definition of the A and P has also been afforded by the new venous severity scoring system,[12] which was developed by the ad hoc Committee on Outcomes of the AVF to complement CEAP. It includes not only a Clinical Severity Score but a Venous Segmental Score. The latter is based on imaging studies of the leg veins, for example, duplex scan, and the degree of obstruction or reflux (P) in each major segment (A) and forms the basis for the overall score.

This same committee also is pursuing a prospective multicenter investigation of variability in vascular diagnostic laboratory assessment of venous hemodynamics in patients with CVD. The last revision of the venous reporting standards[11] still cites changes in ambulatory venous pressure or plethysmographically measured venous return time (VRT) as objective measures of change. The current multicenter study aims to establish the variability of, and thus limits of "normal" for, the VRT and the newer noninvasive venous tests as an objective basis for claiming significant improvement as a result of therapy, and will hopefully provide improved reporting standards for definitive diagnosis and results of competitive treatments in patients with CVD.

DATE OF CLASSIFICATION

CEAP is not a static classification; the patient can be reclassified at any point in time. Classification starts with the initial visit, but can be better defined after further investigations. A final classification may not be complete until after surgery and histopathologic assessment. We therefore recommend that any CEAP classification be followed by the date; for example, C4b,S,Ep,As,p,Pr (2003-08-21).

LEVEL OF INVESTIGATION

A precise diagnosis is the basis for correct classification of the venous problem. The diagnostic evaluation of the patient with CVD can be logically organized into one or more of three levels of testing, depending on the severity of the disease:

Level I: The office visit with history and clinical examination, which may include use of a hand-held Doppler

Level II: The noninvasive vascular laboratory, which now routinely includes duplex color scanning, with some plethysmographic method added as desired

Level III: Invasive investigations or more complex imaging studies including varicography, ascending and descending venography, venous pressure measurements, spiral CT scan, or MRV

We recommend that the level of investigation (L) should also be added to the classification, for example, C2,4b,S,Ep,As,p,Pr (2003-08-21,L II).

BASIC CEAP

A new basic CEAP is offered here. Use of all components of CEAP is still encouraged but unfortunately many physicians merely use only the C-classification, which is just a modest advance beyond the previous classifications and is based solely on the clinical appearance. Venous disease is complex, but can be described by use of well-defined categorical descriptions. For the practicing physician, CEAP can be a valuable instrument for correct diagnosis to guide treatment and assess prognosis. In modern phlebological practice the vast majority of patients will have a duplex scan of the venous system of the leg, which largely will define the E, A, and P categories.

Nevertheless, it is recognized that the merits of using the *full* (advanced) CEAP classification system hold primarily for the researcher and for standardized reporting in scientific journals. It allows grouping of patients so that the same types of patients can be analyzed together, and such subgroup analysis allows their treatments to be more accurately assessed. Furthermore, reports using CEAP can be compared with one another with much greater certainty. This more complex classification, for example, also allows any of the 18 named venous segments to be identified as the location of venous pathology. Take a patient with pain, varicose veins, and lipodermatosclerosis where duplex scan confirms primary reflux of the GSV and incompetent perforators in the calf. The classification here would be C2,4b,S, Ep, As,p, Pr2,3,18.

Although the detailed elaboration of venous disease in this form may seem unnecessarily complex, even intimidating, to some clinicians, it provides universal understandable descriptions that may be essential to investigators in the field. To serve the needs of both, the full CEAP classification, as modified earlier, is retained as advanced CEAP, and the following simplified form is offered as basic CEAP.

In essence, Basic CEAP applies two simplifications: 1) In basic CEAP, *the single highest descriptor can be used for clinical classification*. For example, a patient with varicose veins, swelling, and lipodermatosclerosis would be C4b. The more comprehensive clinical description, in advanced CEAP, would be C2,3,4b.

2) In basic CEAP, where duplex scan is performed, E, A, and P should also be classified using the multiple descriptors recommended, but the complexity of applying these to the 18 possible anatomic segments is avoided in favor of applying the simple s, p, and d descriptors to denote the superficial, perforator, and deep systems. Thus, using basic CEAP, the same patient cited in a previous example (painful varicosities plus lipodermatosclerosis and duplex scan determined reflux involving the superficial and perforator systems) would be classified as C4b,S, Ep, As,p Pr (rather than C2,4b,S, Ep, As,p, Pr2,3,18).

REVISION OF CEAP: SUMMARY

Clinical Classification

C0: No visible or palpable signs of venous disease
C1: Telangiectasias or reticular veins
C2: Varicose veins
C3: Edema
C4a: Pigmentation and/or eczema
C4b: Lipodermatosclerosis and/or atrophie blanche
C5: Healed venous ulcer
C6: Active venous ulcer
S: Symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps, as well as other complaints attributable to venous dysfunction
A: Asymptomatic

Etiologic Classification

Ec: Congenital
Ep: Primary
Es: Secondary (postthrombotic)
En: No venous etiology identified

Anatomic Classification

As: Superficial veins
Ap: Perforator veins
Ad: Deep veins
An: No venous location identified

Pathophysiologic Classification

Basic CEAP:
Pr: Reflux
Po: Obstruction
Pr,o: Reflux and obstruction
Pn: No venous pathophysiology identifiable

Advanced CEAP

Same as basic, with the addition that any of 18 named venous segments can be utilized as locators for venous pathology:

Superficial veins:

1. Telangiectasias/reticular veins
2. Great saphenous vein (GSV) above knee
3. GSV below knee
4. Small saphenous vein
5. Nonsaphenous veins

Deep veins:

6. Inferior vena cava
7. Common iliac vein
8. Internal iliac vein
9. External iliac vein
10. Pelvic: gonadal, broad ligament veins, other
11. Common femoral vein
12. Deep femoral vein
13. Femoral vein
14. Popliteal vein
15. Crural: anterior tibial, posterior tibial, peroneal veins (all paired)
16. Muscular: gastrocnemial, soleal veins, other

Perforating veins:

17. Thigh
18. Calf

Example: A patient presents with painful swelling of the leg and varicose veins, lipodermatosclerosis, and active ulceration. Duplex scanning on May 17, 2004, showed axial reflux of GSV above and below the knee, incompetent calf perforators, and axial reflux in the femoral and popliteal veins. No signs of postthrombotic obstruction.

- Classification according to basic CEAP: C6,S, Ep, As,p,d, Pr
- Classification according to advanced CEAP: C2,3,4b,6,S, Ep, As,p,d, Pr2,3,18,13,14 (2004-05-17, LII)

REVISION OF CEAP—AN ONGOING PROCESS

With improvement in diagnostics and treatment there will be continued demands to adapt the CEAP classification to better serve future developments. There are several conditions that are not included in the CEAP classification but that can influence the management of the patients:

- Combined arterial/venous etiology
- Postthrombotic lymphedema
- Ankle ankylosis with atrophy of the calf
- Venous aneurysms
- Venous neuropathy
- Corona phlebectatica
- Pelvic congestion syndrome
- Morbid obesity

The role of corona phlebectatica (CP) was discussed during the meetings and the Atlantic Ocean was a clear divider. In parts of Europe CP has been used as an early indicator of advanced CVD. Its scientific significance is now under investigation, particularly in France. There is a need to incorporate appropriate new features without too frequent disturbances of the stability of the classification. As one of the committee members (F. Padberg) stated in our deliberations, “It is critically important that recommendations for change in the CEAP standard be supported by solid research. While there is precious little that we are recommending which meets this standard, we can certainly emphasize it for the future. If we are to progress we should focus on levels of evidence for changes rather than levels of investigation. While a substantial portion of our effort will be developed from consensus opinion, we should still strive to achieve an evidence-based format.”

Acknowledgment

Part of this article was previously published in Eklöf B, Rutherford RB, Bergan JJ, Carpentier P, Gloviczki P, Kistner RL et al., for the American Venous Forum International Ad Hoc Committee for Revision of the CEAP classification. Revision of the CEAP classification for chronic venous disorders: Consensus statement, J. Vasc. Surg. 2004. 40:1248–1252.

The author wishes to thank the Society for Vascular Surgery for permission to reproduce the relevant section.

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C H A P T E R

12

Risk Factors, Manifestations, and Clinical Examination of the Patient with Primary Venous Insufficiency

JOHN BERGAN

Knowledge of the risk factors that enter into causation of primary venous insufficiency provides an understanding that aids in care of the patient. There are risk factors, such as heredity, female gender, and aging, that cannot be altered (see Table 12.1). There are others, such as pregnancy, that are acquired but cannot be modified, and there are those with little or no influence, such as smoking, hypercholesterolemia, vitamin intake, and leg crossing. These and the historical and largely abandoned physical tests of the patient with venous insufficiency are the subject of this chapter.

HEREDITY

Although development of varicose veins usually can be ascribed to many conditions, conventional examinations may not disclose the apparent source of the high-pressure leak from the deep to the superficial system.[1] Therefore other inherent factors such as vein wall weakness, increased primary valvular dysfunction or agenesis, and other genetic factors may enhance the development of varicose veins.

In an extensive study in France, 134 families were examined. Of these, 67 were families with patients with varicose veins, and 67 were control families without familial varicose veins. A total of 402 subjects were examined and the results demonstrated a prominent role of hereditary in the development of varicose veins ($p < .001$). For the children, the risk of developing varicose veins was 90% when both parents were afflicted. When only one parent was affected, the risk of developing varicose veins was 25% for men and 62% for women. The overall risk of varicose vein development is 20% when neither parent is affected by varicosities.[2]

A familial tendency toward the development of varicose veins has been described in many population groups.[3,4] This may also be demonstrated by the development over time of varicose veins bilaterally when patients with unilateral varicose and telangiectatic veins are followed for 10 years.[5] A limited study of 50 patients with varicose veins in Great Britain disclosed a simple dominant type of inheritance.[6] Only 28% of patients had no family history of varicose veins. In Scandinavia, questionnaires completed by 124 women with varicose veins disclosed a 72% prevalence of varicose veins of an autosomal type in the women's siblings.[7] Of these cases, 28% were of a recessive pattern. Troisier and Le Bayon examined 154 families with 514 descendants. They found that if both parents had varicose veins, 85% of children had evidence of varicose veins, whereas 27% of the children were affected if neither parent had varicose veins, and 41% of the children were affected if one parent had varicosities. These authors conclude that the inheritance of varicose disease is recessive. However, some studies have not found a significant familial tendency.[8,9]

A single study on unselected twins found that 75% of 12 monozygotic pairs were concordant with regard to varicose veins. Of 25 dizygotic, same-sexed pairs, 52% had varicose veins.[10]

Other studies have found more of a multifactorial inheritance. In a detailed study from Sweden of 250 probands of patients with varicose veins requiring treatment, the overall frequency of varicose veins in female relatives was 43%, compared with 19% in male relatives.[11]

The absence of venous valves in the external iliac and femoral veins has been shown to be a marker of varicose veins in a limited radiographic study of 12 male volunteers, some with and some without varicose veins,[12] and in a

TABLE 12.1 Risk Factors for Varicose Veins and Telangiectasias

Certain
Heredity
Female Gender
Pregnancy
Aging
Conjectural
Diet
Abdominal Straining
Tight Clothing
Leg Crossing

venous Doppler study of 54 patients with varicose veins.[12] In addition, a simple dominant mode of inheritance has been reported in 14 patients with congenital partial or total absence of venous valves of the leg.[13] Thus this genetic predisposition may be the result of multiple factors, and the subsequent development of varicose veins may depend on one or more occupational or hormonal factors.

Recent studies on varicose and normal veins using gene expression profiling based on cDNA microarray analysis suggest that pathways associated with fibrosis and wound healing may be altered in varicose veins.[14] Whether the upregulated varicose vein genes are a sequel to the changes in the varicose vein wall rather than a primary contributing factor to varicose pathogenesis awaits additional study.

PREGNANCY

Pregnancy typically is associated with secondary valvular incompetence. Many epidemiologic studies have found a significantly increased incidence of varicose veins in women who have been pregnant.[15] However, some epidemiologic studies have failed to confirm this association when the effect of age is controlled.[16] Varices are often first noted during pregnancy and are exceedingly rare before puberty. Indeed, population studies have found that only 12% of women with varicose veins have never been pregnant.[17]

In pregnancy, hormonal factors are primarily responsible for venous dilation. As many as 70% to 80% of patients develop varicose veins during the first trimester when the uterus is only slightly enlarged. In the second trimester, 20% to 25% of patients develop varicose veins, and 1% to 5% of patients develop them in the third trimester.[18,19]

Varicose veins of the legs are first apparent as early as six weeks into gestation, a time when the uterus is not yet large enough to significantly impede venous return from the leg veins. Mullane[20] notes that symptoms of varicose veins can be the first sign of pregnancy and can occur even before the first missed menstrual period. This confirms observations of many multiparous women and argues for a profound influence of progesterone on venous dilation and valvular insufficiency.

AGING

The incidence of varicose veins increases with age, therefore vein wall damage should be more pronounced in the veins of older patients. An autopsy study of the popliteal vein in 127 persons demonstrated diffuse changes, with an increase in connective tissue in the media that become most pronounced in the fifth decade and are progressive thereafter. This is associated with the loss of muscle cells in the media.[21] The finding correlated with an abnormality in the physical property of axial tension testing in 93 specimens of saphenous veins from 22 patients harvested during coronary bypass surgery.[22] However, one study of 31 normal veins and 41 varicose veins in patients and autopsy samples ranging in age from 25 to 92 failed to disclose an age-related difference.[23] The latter study concluded that varicose veins were a predetermined disease unrelated to aging effects.

THEORETICAL RISK FACTORS

One popular hypothesis for the development of varicose veins is Western dietary and defecation habits, which cause an increase in intraabdominal pressure. Population studies have demonstrated that a high-fiber diet is evacuated within an average of 35 hours.[24] In contrast, a low-fiber diet has an average transit time of 77 hours. An intermediate diet has a stool transit time of 47 hours.

Defecatory straining induced by Western-style toilet seats has also been cited as a cause of varicose veins, in contrast to the African custom of squatting during defecation.[25,26]

An association between prostatic hypertrophy, inguinal hernia, and varicose veins may be caused by straining at micturition with a resultant increase in intraabdominal pressure.

Another mechanism for increasing distal venous pressure by proximal obstruction is the practice of wearing girdles or tight-fitting clothing. A statistically significant excess of varicose veins is noted in women who wear corsets compared with women who wear less constrictive garments.

Leg crossing and sitting on chairs are two other potential mechanisms for producing a relative impedance in venous return. Habitual leg crossing is commonly thought to result in extravenous compression, but this has never been scientifically verified.

Most,[27] but not all,[28] studies have found that obesity is associated with the development of varicose veins. Careful examination of some of these epidemiologic studies shows that when the patient's age is correlated with obesity, the

statistical significance is eliminated. Varices may be secondary to decreased exercise and associated medical problems specific to obesity such as hypertension, diabetes, hypercholesterolemia, and sensory impairment.

Finally, it commonly is noted that occupations that require standing for prolonged periods have an increased incidence of varicose veins. This may be exacerbated by tall height, although this factor has not been supported by other studies.

VALVE REMODELING

Our interest and focus on the venous valve dysfunction as a fundamental cause of distal venous hypertension began with unpublished observations using angioscopy. The angioscope provided a direct view of the internal architecture of saphenous veins. Patients taken to surgery who demonstrated preoperative reflux verified by duplex ultrasound showed a variety of pathologic lesions in the valves themselves. The first indication was a relative paucity of valves. The observation of decrease in number of GSV valves was reported by Cotton in 1961.[29] Next, we encountered actual valve lesions. These observations were an extension of those reported by Hoshino et al.,[30] who classified valve damage in the saphenous vein into three categories ranging from stretched commissures to perforations and valve splitting.

From the preceding observations we suggest that the earliest valve defects are an increase in the commissural space, which allows reflux on the border of the vein. This may be one of the earliest causes of reflux in varicose veins. Later, thinning, elongation, stretching, splitting, and tearing of the valves develop. The latest stages are thickening, contraction, and possibly even adhesion between valves. These observations have been confirmed by Van Cleef et al.[31] Although we have proposed that this valve damage is acquired and causes axial reflux as well as outflow through check valves in perforating veins, others have proposed that the cause of primary venous insufficiency is an actual reduced number of valves in the saphenous system.[32]

The angioscopic observations could be confirmed by gross morphologic studies that, when extended to microscopic observations using monoclonal antibody labeling, have demonstrated monocytic infiltration into damaged venous valves.[33] Others have found leukocytic infiltration into varicose veins and have called attention to the fact that the cells observed release vasoactive substances, including histamine, tryptase, prostaglandins, leukotrienes, and cytokines. Observations in patients led to the conclusions that venous hypertension was related to leukocytic infiltration on the cranial surfaces of the venous valve and venous wall and that leukocytes there were greater in quantity than on the caudal portion of valve leaflets and venous wall.[34]

Therefore a model of venous hypertension was developed in which microvessels in rat mesentery were examined microscopically. Venous occlusion and subsequent venous hypertension were produced by pipette blockade of venules about 40 μm in diameter. Videomicroscopy revealed early signs of inflammation, such as progressive leukocyte rolling, adhesion, and subsequent migration as well as parenchymal cell death.

This inflammatory sequence occurred early during the phase of venous hypertension and progressed further after release of the occlusion. The model showed that venous occlusion with elevation of the hydrostatic pressure caused a highly injurious process for the surrounding tissues. It was accompanied by formation of microhemorrhages on the high-pressure side of the post capillary venule and rolling and adhesion of leukocytes on the venular endothelium.

van Bemmelen et al.[35] created a model of venous hypertension by performing arteriovenous fistulas in Wistar rats using microsurgical techniques. Valvular incompetence was seen as early as one day after creation of the arteriovenous fistula, and valvular structural changes were noticeable within two months of production of venous hypertension. Elongation of the cusps was observed. Separation and leakage of the cusps were encountered along the entire valvular free border, and, in later stages beyond four months, valve areas became difficult to recognize because commissures were lost and bulging of the valve sinus disappeared.

We have pursued this line of investigation and have reproduced the human observations in the animal model.[36,37,38]

Another model of venous hypertension has been produced by Lalka. This model creates venous hypertension by ligation of the inferior vena cava, the common iliac veins, and the common femoral veins. This preparation elevates rat hind limb venous pressures compared with forelimb pressures. Myeloperoxidase assay indicates leukocyte trapping in hindleg tissues just as it occurs in humans.

The observations just mentioned suggest that valve damage in venous insufficiency is an acquired phenomenon related to leukocyte and endothelial interactions and an inflammatory reaction. This observation is not universally accepted. A study on 13 valve structures from varicose GSV showed an absence of lymphomonocyte infiltration in 85%, and rare isolated "nonsignificant" inflammatory cells in 15%. However, if this hypothesis is correct, pharmacologic intervention to block leukocyte adhesion, activation, and subsequent valve damage may be a possibility.

SYMPTOMS OF PRIMARY VENOUS INSUFFICIENCY

It is well known that the presence and severity of symptoms do not correlate with the size or severity of the varicose veins present. Symptoms usually attributable to varicose veins include feelings of heaviness, tiredness, aching,

TABLE 12.2 Symptoms of Varicose Veins and Telangiectasias

Aching Heaviness (on standing, prolonged sitting)
Aching Pain (on standing, prolonged sitting)
Burning (venous neuropathy)
Itching (cutaneous inflammation)
Nocturnal Cramps (recumbent edema reduction)

TABLE 12.3 Tests of Historic Interest

Trendelenburg Test
Cough Test
Schwartz Test
Perthes' Test

burning, throbbing, itching, and cramping in the legs (see Table 12.2). These symptoms are generally worse with prolonged sitting or standing and are improved with leg elevation or walking. A premenstrual exacerbation of symptoms is also common. Generally, patients find relief with the use of compression in the form of either support hose or an elastic bandage. Weight loss or the commencement of a regular program of lower extremity exercise may also lead to a diminution in the severity of varicose vein symptoms. Clearly, these symptoms are not specific, as they may also be indicative of a variety of rheumatologic or orthopedic problems. However, their relationship to lower extremity movement and compression is usually helpful in establishing a venous origin for the symptoms. Significant symptoms suggestive of venous disease should prompt further evaluation for valvular insufficiency and calf muscle pump dysfunction. If a venous etiology is suspected but all examinations are negative, repeat examination during a symptomatic period is warranted and often fruitful.

The recent development of an extremely painful area on the lower leg at the ankle associated with an overlying area of erythema and warmth may be indicative of lipodermatosclerosis, which may be associated with insufficiency of an underlying perforator vein, and examination for this lesion should be performed. Lipodermatosclerosis may precede ulceration and has been shown to be improved by stiff compression and certain pharmacologic interventions.

Patients with a history of iliofemoral thrombophlebitis who describe "bursting" pain with walking may be suffering from venous claudication. In these patients an evaluation for persistent hemodynamically significant obstruction, possibly treatable with angioplasty and stenting, may be in order.

PHYSICAL EXAMINATION

Using no special equipment, the practitioner can obtain a degree of information regarding overall venous outflow from the leg, the sites of valvular insufficiency, the presence of primary versus secondary varicose veins, and the presence of DVT. The screening physical examination consists of careful observation of the legs. Any patient with the following conditions should be examined more fully: large varicose veins; bulges in the thigh, calf, or the inguinal region representative of incompetent perforating veins (IPVs) or a saphena varix; signs of superficial venous hypertension such as an accumulation of telangiectasias in the ankle region (corona phlebectatica); or any of the findings suggestive of venous dermatitis (pigmentation, induration, eczema). This includes patients with obvious cutaneous signs of venous disease such as venous ulceration, *atrophie blanche*, or lipodermatosclerosis. An obvious but often forgotten point is the necessity of observing the entire leg and not confining the examination simply to the area that the patient feels is abnormal.

Finally, because the veins of the leg empty into the pelvic and abdominal veins, inspection of the abdomen is very important, since dilation of veins on the abdominal wall or across the pubic region suggests an old iliofemoral thrombus. Dilated veins along the medial or posterior aspect of the proximal thigh or buttocks most often arise from varicosities involving the pudendal or other pelvic vessels, and these can be of ovarian reflux origin.

CLINICAL TESTING

Historically important tests of venous function have been part of the physical examination of venous insufficiency (see Table 12.3). These tests have been laid aside largely because of their lack of specificity and sensitivity. The continuous-wave Doppler examination has replaced most of these tests, and confirmatory duplex testing has relegated them to an inferior role. However, the educated physician who treats venous insufficiency must have knowledge of these tests and their physiologic background, such as the Trendelenburg test or Brodie-Trendelenburg test.

Trendelenburg Test

A tourniquet may be placed around the patient's proximal thigh while the patient is standing. The patient then assumes the supine position with the affected leg elevated 45 degrees. The tourniquet is removed, and the time required for the leg veins to empty, which is indicative of the adequacy of venous drainage, is recorded.

When compared with the contralateral leg, the method just described may demonstrate a degree of venous obstructive disease. Another approach is to elevate the leg while the

patient is supine and to observe the height of the heel in relation to the level of the heart that is required for the prominent veins to collapse. Unfortunately, neither procedure is sufficiently sensitive nor accurate and does not differentiate acute from chronic obstruction, thus being of minimal assistance in current medical practice.

Cough Test

One hand is placed gently over the GSV or SFJ, and the patient is asked to cough or perform a Valsalva maneuver. Simply palpating an impulse over the vein being examined may be indicative of insufficiency of the valve at the SFJ and below to the level of the palpating hand.

Percussion/Schwartz Test

One hand is placed over the SFJ or SPJ, and the other hand is used to tap very lightly on a distal segment of the GSV or SSV. The production of an impulse in this manner implies insufficiency of the valves in the segment between the two hands. Confirmation of the valvular insufficiency can be achieved by tapping proximally while palpating distally. This test can also be used to detect whether an enlarged tributary is in direct connection with the GSV or SSV by palpating over the main trunk and tapping lightly on the dilated tributary, or vice versa. The presence of a direct connection results in a palpable impulse being transmitted from the percussing to the palpating hand. As might be expected, these tests are far from infallible.

Perthes' Test

The Perthes' test has several uses, including distinguishing between venous valvular insufficiency in the deep, perforator, and superficial systems and screening for DVT. To localize the site of valvular disease, the physician places a tourniquet around the proximal thigh with the patient standing. When the patient walks, a decrease in the distension of varicose veins suggests a primary process without underlying deep venous disease because the calf muscle pump effectively removes blood from the leg and empties the varicose veins. Secondary varicose veins do not change caliber (if there is patency of the deep venous system) because of the inability to empty blood out of the veins as a result of impairment of the calf muscle pump. In the setting of a current DVT, they may increase in size. If there is significant chronic or acute obstructive disease in the iliofemoral segment, the patient may note pain (venous claudication) as a result of the obstruction to outflow through both the deep and superficial systems. The Perthes' test is now of more historical than actual clinical importance.

Acknowledgment

Much of the material in this manuscript was derived and modified from the scholarly research of Mitchel Goldman, MD, and was published in his volume on Sclerotherapy.

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CHAPTER

13

Sclerosing Solutions

CRAIG FEIED

GOALS OF SCLEROTHERAPY

When we treat varicosities and telangiectasias, we want to remove or obliterate the abnormal vessels that carry retrograde flow, without damaging adjacent or connected vessels that carry normal antegrade flow. Obliterating a vessel is not easy: a small amount of damage will produce intravascular thrombus, but thrombosis alone usually does not result in obliteration of the vessel. Intact endothelium aggressively lyses thrombus, and a thrombosed vessel with intact endothelium will not be sclerosed (see Figure 13.1).

RECANALIZATION OF THROMBOSED VESSELS

Vascular fibrosis and obliteration occur only in response to irreversible endothelial cellular destruction and exposure of the underlying subendothelial cell layer. If an injected sclerosant is too weak, there may be no endothelial injury at all. If the sclerosant is a little stronger, the vessel is damaged, but recanalization occurs and an incompetent pathway for retrograde blood flow persists. If the injected sclerosant is too strong, the varicose vessel endothelium is destroyed, but the sclerosant also flows into adjacent normal vessels and causes damage there as well. The key goal is to deliver a *minimum* volume and concentration of sclerosant that will cause irreversible damage to the endothelium of the abnormal vessel, while leaving adjacent normal vessels untouched. It is important to protect normal superficial vessels, and it is critically important to avoid injuring the endothelium of deep veins, because deep vein thrombosis places patients at risk of death from thromboembolism, as well as causing permanent disability from chronic deep venous valvular insufficiency. The successful treatment of varicosities and telangiectasias by chemical sclerosis depends upon our ability to produce vascular endothelial damage that is irreversible in the area under treatment, but that does not extend to adjacent normal vessels.

To limit endothelial injury to a controlled area, we exploit differences in flow dynamics between the abnormal veins being injected with sclerosant and the adjacent normal vessels that should not be sclerosed. A thorough understanding of the mechanism of action of the sclerosing agent is essential, as is a firm grasp of the biophysical principles underlying the techniques of sclerotherapy.

VOLUME DILUTION AND PATIENT POSITIONING

Sclerosant is diluted with blood as it diffuses away from the site of injection, thus if a strong sclerosant is injected there will be three zones of action (see Figure 13.2). In Zone 1, vascular endothelium is irreversibly injured: the vessel will be fully sclerosed and eventually will be completely replaced by a fibrous tissue. In Zone 2, vascular endothelium is injured, and the vessel will be partially or completely thrombosed but will eventually recanalize. In Zone 3, the sclerosant will be diluted below its injurious concentration, and there will be no endothelial injury.

DILUTION BY DIFFUSION FROM INJECTION SITE

Because dilution of the sclerosant with blood occurs immediately upon injection, the original injected concentration

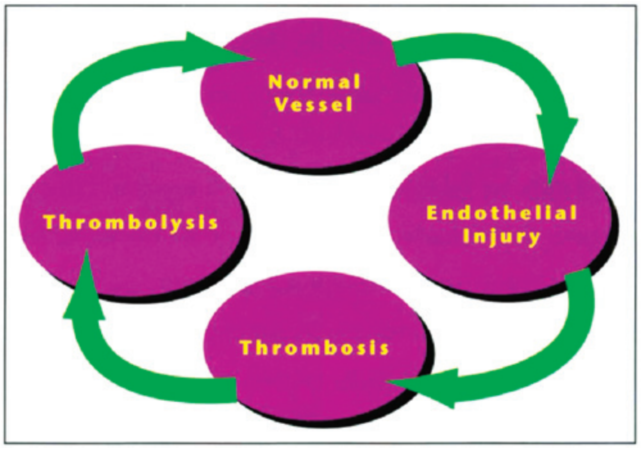

FIGURE 13.1 Normal cycle of healing after minor vessel injury.

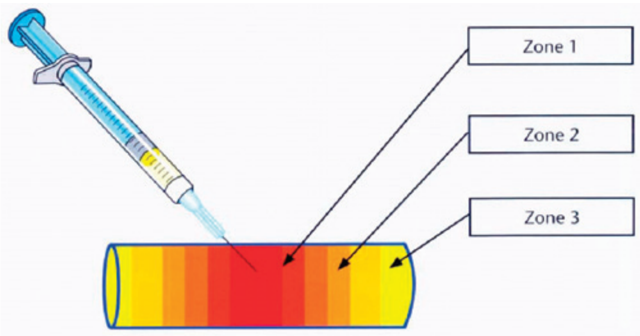

FIGURE 13.2 Zones of injury after dilution by blood volume.

is not as important as the diluted concentration of clerosant at the surface of the endothelium. An injected concentration that is perfectly effective in a spider vein (where sclerosant displaces blood rather than mixing with it) may be ineffective in a reticular feeding vein or a truncal varix simply because dilution reduces the final concentration so low that there will be no endothelial injury whatsoever (no Zone 1 or Zone 2). If the injected concentration is too high, dilution will leave the final concentration so high that endothelial damage will occur where it is not wanted (Zone 1 and Zone 2 are too large). If the injected concentration is just right, dilution will leave a final concentration that is sufficient to injure the local varicose endothelium, but not high enough to damage normal superficial or deep veins (most of the varicose vessel falls into Zone 1, a small amount falls into Zone 2, and all normal vessels fall into Zone 3).

When we select a particular volume and concentration of a chemical agent with which to sclerose a vessel, we are explicitly or implicitly adjusting the injected concentration and volume to take into account the dilution that will occur when the sclerosant is mixed with blood immediately after injection. We also must take into account the further dilution that will occur as the sclerosant flows or diffuses away from the site of injection. The importance of patient positioning in determining dilutional volume often is not properly appreciated by the novice in phlebology.

Because of the cylindrical geometry of blood vessels, the volume contained in a vessel depends on the square of the vessel radius: the volume of any cylinder is calculated as $\pi r^2 (L)$ (where r is the radius and L is the length of the vessel). Vessels collapse to a smaller radius when the legs are elevated, thus the volume contained is reduced dramatically. For this reason, the position of the patient has a very powerful effect on the final diluted concentration of sclerosant at the surface of the vessel endothelium (see Figure 13.3).

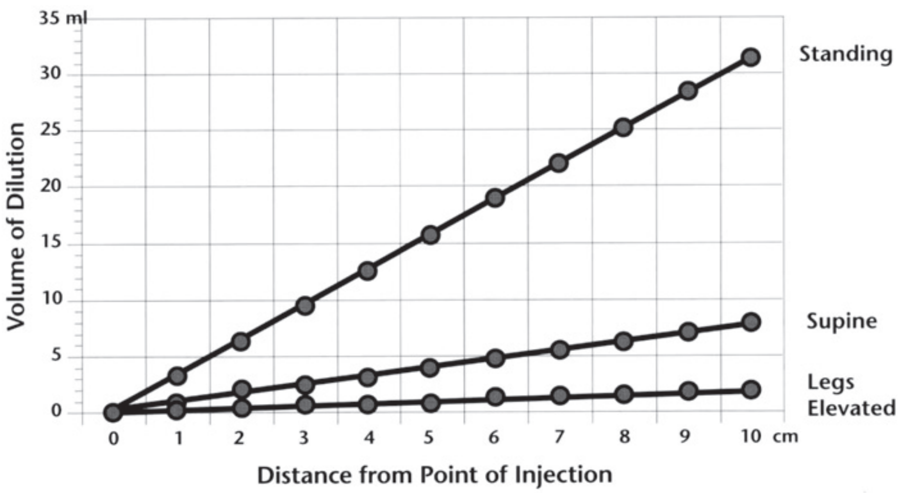

FIGURE 13.3 Volume of dilution and distance from injection point: effect of patient position.

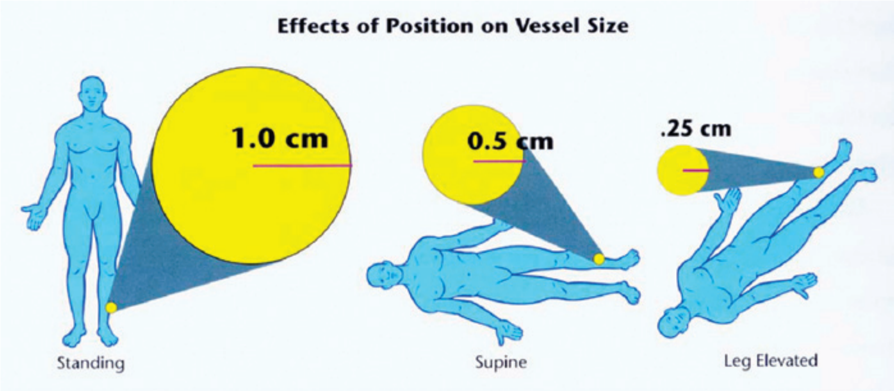

FIGURE 13.4 Varicose vessel radius as a function of position.

EFFECT OF POSITION ON VARICOSE GEOMETRY

For the following sections, refer to Figure 13.4.

Standing

For a standing patient with a superficial varicosity of 2 cm in diameter, the final concentration at a distance from the injection site of 10 cm (4 inches) is 30 times lower than the initial concentration. Doubling the initial concentration serves only to double the final concentration, which will still be 15 times weaker than the concentration in the syringe. In other words, if 1 cc of a 3% solution is injected, the final concentration at the endothelial surface is 1% at a distance of 1 cm from the injection point, 0.5% at a distance of 2 cm, 0.25% at a distance of 4 cm, and 0.2% at a distance of 5 cm (2 inches) from the injection point. As we shall see, this means that it is very difficult to achieve sclerosis of a large vessel by injecting detergent sclerosants with the patient in a standing position: if the highest available concentration is injected, the dilution factor may still drop the final concentration below the threshold of effectiveness within 1.5 inches from the injection site.

Supine

What about the supine position? Varicose vessels that bulge when the patient is standing may collapse when the patient is supine, but duplex ultrasound readily demonstrates that the veins are not empty of blood. Both varicose and normal vessels contain a significant volume of blood with the legs extended in the supine position. A bulging varicosity that has a diameter of 2 cm in the standing position may have a diameter of 1 cm in the supine position and of 0.5 cm or less when the legs are elevated as high as possible. With such a patient in the supine position, injection of 1 cc of a 3% solution leads to a final concentration of approximately 1.7% at a distance of 1 cm and a concentration of about 0.6% at a distance of 5 cm (2 inches). This supine technique limits dilution enough to allow successful sclerosis of large vessels using detergent solutions, as long as sufficient concentrations and volumes of sclerosants are injected. The only problem is that if an injection of sclerosant at a high initial concentration is made directly into a perforating vessel, so that sclerosant flows directly into the deep system, dilution within the deep vessel will still permit Zone 1 and Zone 2 endothelial injury for a short distance within the deep vein. This can lead to deep vein valve damage and chronic venous insufficiency, to deep vein thrombosis, and to life-threatening pulmonary embolism.

Legs Elevated

In contrast to the standing and supine positions, when a patient lies supine and the legs are raised vertically so that they are well above the central circulation, most superficial varices collapse to the point where they no longer contain any significant volume of blood. Repeating this calculation for a patient in this position, injection of 1 cc of a 3% solution leads to a final concentration of 2.5% at a distance of 1 cm from the injection, and a final concentration of 1.6% at a distance of 5 cm (2 inches). In fact, the final concentration will still be above 1% at a distance of 10 cm from the injection site. Because the superficial varicosity is collapsed, there is very little dilution with distance as long as the sclerosant stays within the floppy-walled varicosity.

With the increasing use of foamed preparations of sclerosants, another factor must be taken into consideration since the dilution of these medications is significantly reduced. Although all the preceding considerations still play an important role, the distance over which a foamed sclerosant remains at high concentration is markedly increased. Therefore, smaller volumes and/or lower original concentrations should be employed when using a foamed sclerosant.

What happens when sclerosant passes through into normal vessels? Although flow measurements reveal little or no spontaneous flow through varices and smaller superficial veins when the patient is in the leg-up position, a substantial intravenous volume and a substantial rate of flow still persists in the deep veins and in normal larger superficial veins, which have less collapsible walls. This difference in volumes and flow rates may be exploited to cause damage that is almost perfectly localized to superficial varices. If an elevated, empty varicose vessel is perfused with a concentration of sclerosant so low that it is just barely sufficient to cause endothelial injury, then any further dilution will reduce the concentration below the threshold of injury. Because larger superficial vessels and deep vessels continue to carry a volume of blood in the leg-up position, any sclerosant passing into these vessels will immediately be diluted to a safe and noninjurious concentration, sparing the endothelium of vessels that we wish to preserve. Injection of this threshold concentration directly into a perforating vein (or even directly into a deep vein) will not cause any deep vein injury.

TYPES OF SCLEROSANTS

Virtually any foreign substance can be utilized to cause venous endothelial damage. Historical methods for producing venous endothelial trauma have included *a slender rod of iron*, reportedly used by Hippocrates himself; *absolute alcohol*, introduced by Monteggio and by Leroy D'Etoilles in the 1840s; and *ferric chloride*, introduced by Charles-Gabriel Pravaz in 1851. Early sclerosing agents caused many deaths (from sepsis and from pulmonary embolism), as well as a high incidence of allergic reactions, local tissue necrosis, pain, and failed sclerosis.

THE PERFECT SCLEROSANT

The best imaginable sclerosant would have no systemic toxicity. It would be effective only above some threshold concentration, so that its effects could be precisely localized through dilution. It would require a long period of contact to be effective, so that it would be relatively more effective in areas of stasis and relatively safer in the deep veins where there is high flow. It would be nonallergenic. It would be strong enough to sclerose even the largest vessels, yet it would produce no local tissue injury if extravasated. It would not cause staining or scarring. It would not cause telangiectatic matting. It would be perfectly soluble in normal saline. It would be painless upon injection. It would be inexpensive. It would be approved by the United States Food and Drug Administration (FDA).

No currently available sclerosant possesses all the attributes of the perfect sclerosing agent. All currently available sclerosants fall short in one way or another, yet the variety of available agents is such that virtually every situation in which sclerotherapy is indicated can be safely and effectively handled by one or another of the available sclerosants, used alone or in combination.

DETERGENTS

In the 1930s the class of drugs known as detergents, or as fatty acids and fatty alcohols, came into use with the introduction of sodium morrhuate and sodium tetradecyl sulfate. Detergent sclerosants work by a mechanism known as protein theft denaturation, in which an aggregation of detergent molecules forms a lipid bilayer in the form of a sheet, a cylinder, or a micelle, which then disrupts the cell surface membrane and may steal away essential proteins from the cell membrane surface.

The loss of these essential cell surface proteins causes a delayed cell death: when endothelial cell membranes are exposed to detergent micelles, irreversible cellular morphological changes are seen within minutes by scanning electron microscopy, but the fatal cellular changes that are visible by normal light microscopy do not become apparent for many hours. Unlike many other agents, the detergent sclerosants do not cause hemolysis, nor do they provoke direct intravascular coagulation.

Determinants of Activity of Detergent Solutions

Concentration

At low concentrations, most detergent molecules are individually dissolved in solution, and there are very few micellar aggregates. When the concentration reaches some threshold (known as the critical micellar concentration, or CMC) nearly all further detergent molecules added to the solution will enter into micelles. Micelles can cause protein theft denaturation, but individual detergent molecules have no toxicity to the vascular endothelium, thus for each detergent sclerosant, there is some threshold concentration below which the agent causes no injury. This physical property means that detergent sclerosants offer significant benefits over most of the agents previously used, because they are potent agents that nonetheless have a clear-cut threshold below which they have absolutely no injurious effect on venous endothelium.

Temperature

The solubility of detergents is inversely temperature dependent. Detergent molecules are much more soluble in cold solutions than in hot ones. This effect is easily seen in

everyday life: dishwashing detergent produces a large amount of persistent foam in warm water, and cold water rinses away the soapy foam easily. The solubility of sclerosing agents such as polidocanol is likewise much higher in cold solutions, and because single dissolved molecules are ineffective, the strength of the sclerosing effect is higher at warmer temperatures.

Mixing

Detergent micellar formation can reach a maximum level based upon the temperature and upon the concentration of the detergent in solution. Micellar formation is a steric process, however, and the geometry of macroassemblages often prevents maximal micellar formation. The surface area of lipid bilayer structures such as sheets, cylinders, and micelles is maximized when the solution is shaken to produce a foam. Because it is the surface of these structures that causes protein theft denaturation, a solution that has been shaken will be a more effective sclerosant than one that has not. Unfortunately, foamy bubbles that are injected into spider veins or varicose veins can pass through a patent foramen ovale to lodge in the ocular and cerebral circulation, where they have produced temporary ischemic attacks with temporary blindness and other central nervous system effects.

Currently Available Detergent Agents

Sodium Morrhuate

This detergent sclerosant is made of a mixture of saturated and unsaturated fatty acids extracted from cod liver oil. It was introduced in the 1920s and is still available today. Because it was in general use before there was any requirement to demonstrate safety or efficacy, it has been exempted from the need for approval by the FDA for sale in the United States, but there are several problems with the product that make it a less than ideal agent for sclerotherapy. It is a biological extract rather than a synthetic preparation, and the composition varies somewhat from lot to lot. Its components have been incompletely characterized, and a significant fraction of its fatty acids and alcohols are of chain lengths that probably do not contribute to its effectiveness as a sclerosant. It is unstable in solution, causes extensive cutaneous necrosis if extravasated, and has been responsible for many cases of anaphylaxis.

Ethanolamine Oleate

Ethanolamine oleate, a synthetic preparation of oleic acid and ethanolamine, has weak detergent properties because its attenuated hydrophobic chain lengths make it excessively soluble and decrease its ability to denature cell surface proteins. High concentrations of the drug are necessary for effective sclerosis, and its effectiveness in esophageal varices depends upon mural necrosis. Allergic reactions are uncommon, but there have been reports of pneumonitis, pleural effusions, and other pulmonary symptoms following the injection of ethanolamine oleate into esophageal varices. Like sodium morrhuate, this agent was exempted from the need for approval by the Food and Drug Administration (FDA) for sale in the United States. The principal disadvantages of the drug are a high viscosity that makes injection difficult, a tendency to cause red cell hemolysis and hemoglobinuria, the occasional production of renal failure at high doses, the possibility of pulmonary complications, and a relative lack of strength compared with other available sclerosants.

Sotradecol

Sodium tetradecyl sulfate (sodium l-isobutyl-4-ethyloctyl sulfate) is a synthetic long chain fatty acid that has seen extensive industrial use as a synthetic surfactant (soap). It is sold for medical use as a solution of up to 3% concentration with 2% benzoyl alcohol used as a stabilant. It is effective as a venous sclerosing agent in concentrations from 0.1% to 3%. Like sodium morrhuate and ethanolamine oleate, it was "grandfathered" by the FDA for sale in the United States, but its approval was rescinded at the request of the manufacturer, not for reasons of product safety. In the United States, it is currently available only through compounding pharmacies. Unlike sodium morrhuate, sodium tetradecyl sulfate has proven to be a reliable, safe, and effective sclerosant. The principal clinical problems with the drug are a tendency to cause hyperpigmentation in up to 30% of patients, a significant incidence of epidermal necrosis upon extravasation of higher concentrations, and occasional cases of anaphylaxis.

Polidocanol

Polidocanol (hydroxy-polyethoxy-dodecane) is a synthetic long-chain fatty alcohol. All commercially available formulations contain some small quantity of ethanol. The drug originally was developed and marketed in the 1950s under the name Sch 600 as a non-amide, non-ester local anesthetic, was first used as a sclerosing agent in Germany in the 1960s, and was quickly adopted for that use in most countries. The drug was never approved by the FDA for sale in the United States as a sclerosing agent. It is available from local compounding pharmacies. Polidocanol is painless upon injection, does not produce necrosis if injected intradermally, and has been reported to have a very low incidence of allergic reactions. The drug has been intensely studied and extremely well characterized, and has a high

therapeutic index. The LD50 in rabbits is 200 mg/kg (approximately five times greater than that of novocaine), and the LD50 in mice is even greater, at 1200 mg/kg. For human use the German manufacturer of polidocanol recommends a maximum daily dose of 2 mg per kg, although at least one author has reported the routine use of much higher doses. For all its advantages, polidocanol is not without problems as a sclerosant. Occasional anaphylactic reactions have been reported. In some patients it may produce hyperpigmentation, although to a lesser extent than many other agents. Telangiectatic matting after sclerotherapy with polidocanol is as common as with any other agent.

Glycerin

Glycerin is a polyalcohol that often is considered a chemical irritant sclerosant. It is classified here with the detergents because it is similar to the detergents in the way it causes cell surface protein denaturation. It is very popular in Europe, used as a 72% chromated solution marketed under the name Scleremo. It has not been approved by the FDA, and its use in this country only recently has become common. Compared to other sclerosants it is a very weak sclerosant (it is approximately $\frac{1}{4}$ the strength of polidocanol at the same concentration and volume) and is principally useful in the sclerosis of small vessels. Its principal advantage is that it rarely causes hyperpigmentation or telangiectatic matting, and that it very rarely causes extravasation necrosis. The main problems with glycerin are that it is hard to work with because it is extremely viscous, that it can be quite painful on injection, that the chromate moiety is highly allergenic, and that occasionally it has been reported to cause ureteral colic and hematuria.

HYPERTONIC AND IONIC SOLUTIONS

Strong solutions of hypertonic saline and other salt solutions are part of a class of solutions that often are referred to as osmotic sclerosants. These solutions have long been regarded as causing endothelial death by osmotic cellular dehydration. Although it is true that osmotic dehydration at the point of injection is sufficient to rupture red blood cells and to dehydrate some nearby endothelial cells, the evidence suggests that these sclerosants are effective even after dilution has reduced the osmotic gradient far too low to account for the effects seen. Thermodynamic and physical chemical calculations suggest that these and other strong ionic solutions probably work by causing conformational denaturation of cell membrane proteins *in situ*. Like the detergents, they can be diluted to the point where they have no further cellular toxicity.

Hypertonic and Ionic Solutions Currently in Use

Hypertonic Saline

Hypertonic solutions of saline became popular agents for sclerotherapy after they were adopted for that use by Linser in 1926. The most common preparations are a 20% or 23.4% solution. The principal advantage of the agent is the fact that it is a naturally occurring bodily substance with no molecular toxicity. It has not been approved by the FDA for use in sclerotherapy, but it has been used successfully for that purpose by several generations of physicians. There are several reasons why it is not universally accepted as a desirable sclerosing agent. Because of dilutional effects, it is difficult to achieve adequate sclerosis of large vessels without exceeding a tolerable salt load. It can cause significant pain on injection, and leg cramping after a treatment session. If extravasated, it almost invariably causes significant necrosis. Because it causes immediate red blood cell hemolysis and rapidly disrupts vascular endothelial continuity, it is prone to cause marked hemosiderin staining that is not very cosmetically acceptable. All these problems can be overcome to some extent by meticulous technique and with experience, but patient satisfaction remains lower than with some other available agents. In an effort to reduce the complications, hypertonic saline has been mixed with procaine and heparin in a compound known as Heparsol. This approach has not proven effective, and is used rarely today.

Sclerodex

Sclerodex is a mixture of 25% dextrose and 10% sodium chloride, with a small quantity of phenethyl alcohol. Primarily a hypertonic agent, its effects are similar to those of pure hypertonic saline, but the reduced salt load offers certain benefits. It is not approved by the FDA for sale in the United States. Like pure hypertonic saline, it is somewhat painful on injection, and epidermal necrosis continues to be the rule whenever extravasation occurs.

Polyiodinated Iodine

Polyiodinated iodine (Variglobin, Sclerodine) is a mixture of elemental iodine with sodium iodide, along with a small amount of benzyl alcohol. It is rapidly ionized and rapidly protein-bound when injected, and most likely works by localized ionic disruption of cell surface proteins *in situ*. *In vivo* conversion of ionized iodine to iodide renders the solution ineffective as a sclerosant, thus localizing the sclerosing effects to the immediate area of injection. The agent is not approved by the FDA for sale in the United States, but is

widely used in Europe. The problems with this agent are its high tendency to cause extravasation necrosis, its limited effectiveness at a distance from the injection site, and the risks of anaphylaxis and of renal toxicity that are associated with ionic iodinated solutions.

CELLULAR TOXINS

Other chemical sclerosants exist that probably act by a direct or indirect chemical toxicity to endothelial cells: by poisoning some aspect of cellular activity that is necessary for endothelial cell survival. Such agents are less useful to the extent that they also poison other bodily cells. They also lack another of the key attributes of a good sclerosant: they remain toxic to some degree even after extreme dilution, so that there is no real threshold below which injury will not occur.

SUMMARY

The guiding principle of modern sclerotherapy is to cause irreversible endothelial injury in the desired location, while avoiding any damage to normal vessels that may be interconnected with the abnormal vessel we are treating. Our aim is to deliver the minimum volume and minimum concentration of the most appropriate sclerosant, and to inject it under conditions that will achieve the minimum effective exposure. Sclerosant concentration, volume, temperature, mixing, and patient positioning are more important in this endeavor than the choice of the actual sclerosing agent. With attention to these details, an accomplished phlebologist can achieve good results with virtually any currently available sclerosing agent.

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CHAPTER

14

Sclerotherapy Treatment of Telangiectasias

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INTRODUCTION

Isolated small reticular veins and telangiectasias often cause severe symptoms that are worsened by prolonged standing or sitting and may be relieved by wearing support hose or by elevation of the legs.[1] Vein size alone does not predict the presence of symptoms. Vessels causing symptoms may be as small as 1 mm in diameter or less.[2] Besides symptoms of pain, burning, and fatigue, women typically curtail their activities and modify their lifestyles to avoid situations in which their legs are easily seen. Sclerotherapy not only offers the possibility of remarkably good cosmetic results, but also has been reported to yield an 85% reduction in symptoms.[1] Prior experience with venipuncture helps very little with treatment of larger veins and is completely irrelevant in the treatment of the smallest veins. Successful treatment requires the correct technique, the correct diagnosis, and the correct treatment plan for the type and size of vein to be treated.

TELANGIECTASIA FROM RETICULAR VEINS

Telangiectasia can develop due to reflux from reticular veins, thin-walled blue superficial venules that are part of an extensive network of the lateral subdermic venous system; a system that is separate from the saphenous system. A typical network is shown in Figure 14.1. Reticular veins associated with telangiectasia are commonly called "feeder" veins. Both handheld Doppler and duplex ultrasound has been used to map the path of transmission of venous hypertension from small reticular veins into telangiectasia.[3,4]

ISOLATED ARBORIZING WEBS

High-pressure reflux through failed valves is at the root of nearly all telangiectatic webs, although there are some exceptions due to A-V malformations or shunts. This has been estimated to occur approximately 1 in 20 times, although this may be a high estimate.[5] Typically, localized valve failure will produce arborizing networks of dilated cutaneous venules that are direct tributaries of underlying larger veins. Arborization occurs through a recruitment phenomenon in which high pressure causes dilatation of a venule, failure of its valves, and transmission of the high pressure across the failed valves into an adjacent vein. Treatment of an arborizing system must be directed at the entire system, because if the point source of reflux is not ablated, the web will rapidly recur.

PRETREATMENT INSTRUCTIONS

Patients are told to wear shorts and not to use moisturizers or shave their legs on the day of treatment. Shaving the leg may cause erythematous streaks, making it difficult to visualize patterns of reticular and telangiectatic veins. Use of moisturizers causes poor adhesion of tape used to secure compression following injections and causes slower evaporation of alcohol used to prep the leg. Patients are encouraged to eat at least a small meal beforehand in order to minimize vasovagal reactions.

FIGURE 14.1 Typical telangiectatic web-reticular vein complex of the lateral subdermic venous system.

FIGURE 14.2 Foam mixture of STS 0.1% comprised of liquid sclerosant agitated with air at a ratio of 1 part liquid to 4 parts air. Here the foam is seen injected into a reticular vein. Foam is visualized in the vein up to arrow.

FIRST TREATMENT TEST

The first treatment session usually is limited to a small number of sites in order to observe the patient for any allergic reactions and the ability to tolerate the burning or cramping of a hypertonic solution, to judge the effectiveness of a particular concentration and class of sclerosing agent, and to observe the ability to comply with compression. It also serves to familiarize the patient with the treatment, treating physician, clinic surroundings, and the sensation of the fine needle. This allows more extensive treatment on the second visit with the patient being familiar with the technique and surroundings. The test site also complies with the suggestion in the package insert of sodium tetradecyl sulfate (STS) (Sotradecol™, Bioniche Pharma, Belleville, Ontario).

When the patient returns in four to eight weeks, the test site or limited treatment area is compared with pretreatment photographs. Any side effects such as matting and pigmentation can be explained to the patient. Reasonable time intervals for clearance of treated vessels can be reinforced. At each session, all sites treated are noted in anatomic diagrams in the chart.

TREATMENT PLAN

With increasing experience and recognition of common patterns, injection sites are based on known patterns of reflux. For example, reticular veins usually feed a group of telangiectasias on the lateral thigh from a varicose lateral subdermic venous system. During the treatment session, treatment would begin with reticular veins from which reflux is suspected to arise and would proceed along the course of the reticular vein, with injections every 3–4 cm along the feeder.

Our typical treatment regimen is to foam or agitate STS at 0.1 to 0.2% using a ratio of one part sclerosant to four parts air. This foam mixture is injected into reticular veins that are directly connected to visible telangiectasias (see Figure 14.2). It is not advisable to treat every reticular vein of the thigh; only those reticular veins visibly connected to a telangiectatic web should be targeted.

As sclerosing solution/foam flows away from the point of injection, it is clearly seen for a distance of several centimeters before it is diluted by blood and becomes less potent.

When injecting a reticular vein, the sclerosing foam is sometimes seen flowing into the telangiectasia. When this is observed, the telangiectasias do not need to be injected directly. Similarly, sclerosing solution injected into a telangiectasia may be seen flowing into the feeder vein, but reticular veins usually still need to be injected directly, because it is difficult to deliver an effective volume and concentration of sclerosant foam to the reticular vein indirectly.

TECHNIQUE

The technique used for injection of small reticular feeder veins is the direct cannulation technique used for the injection of larger, deeper reticular veins and varicose veins.

The patient is recumbent in a position that allows convenient access to the reticular veins to be treated. A 3 cc syringe with a 27 or 30 gauge is used, and the needle is bent to an

FIGURE 14.3 The position of the syringe with needle bend in the hands of the injecting physician for injecting reticular and telangiectatic veins. This shows the injection of 72% glycerine into telangiectasias. Some blanching is seen.

angle of 10 to 30 degrees to facilitate cannulation of the vein (see Figure 14.3). The syringe is held in the dominant hand, which rests on the patient's leg, and the needle is advanced at a shallow angle through the skin and into the reticular vein. When the physician feels the typical "pop-through" sensation of piercing the vein, the plunger is pulled back gently until blood return is seen in the transparent plastic hub. Typically one injects up to 2 cc of foamed sclerosant and then massages the solution toward any associated telangiectasias. Injection must stop immediately if any signs of leakage occur or if a bleb or bruising is noted. As the needle is withdrawn, pressure is applied immediately either with cotton ball then tape, or compression bandaging.

The cannulation of a reticular vein can be quite difficult at times, because reticular veins can go into spasm, and may virtually disappear during an attempt at cannulation. It is best to avoid applying alcohol to the skin just prior to treatment as the evaporative cooling may cause venospasm of the reticular vein. Any resistance to injection means the needle tip is not inside the vein. When this happens, the injection should be terminated immediately and the needle withdrawn. Failed cannulation will rapidly produce a bruise at the site of injection.

EQUIPMENT

- Cotton balls soaked with 70% isopropyl alcohol
- Protective gloves
- 1 cc or 3 cc disposable syringes
- 3-way IV stopcock for agitation/foaming
- 30 gauge ½″ disposable transparent hub needles
- Cotton balls or foam pads for compression
- Hypo-allergenic tape (synthetic silk or paper)
- Topical nitroglycerine ointment (2%)
- Sclerosing solutions (stored separately from other injectables in the clinic)
- Magnifying loupes or lenses (2–3×)

The choice of syringe is a personal one. Some phlebologists believe that a 3 cc syringe allows optimal control. Others hold that a 1 cc syringe is preferable because the smaller plunger offers reduced plunger friction and allows smoother control with less jerkiness, but higher pressures may induce quicker vessel rupture. It is worth the effort to try a variety of syringes, as there is a marked difference in plunger friction between different types of syringes and between syringes from different manufacturers.

With use of sodium tetradecyl sulfate (STS), it is recommended to use latex-free syringes. In high enough concentration, STS (0.5% and greater) will dissolve the rubber from the plunger, thereby releasing rubber and rubber products into solution. There is a relatively high and increasing incidence of latex allergy in the general population.[6] Theoretically the risk of a severe allergic reaction may be increased with latex-containing syringes. We have not yet seen allergic reactions to STS in over 500,000 injections since switching to latex-free syringes in 1994.

PATIENT PREPARATION

The patient is recumbent in a position that allows convenient access to the telangiectasias to be treated. If available, a motorized table with height adjustment will facilitate easy access to all regions of the leg. Use of double polarized lighting (InVu Vantage, Syris Scientific, Grey, ME) has also proven to be helpful (see Figure 14.4). The neck and back position of the treating physician must be optimal to avoid injury over the long term to the physician. Indirect lighting is best as harsh halogen surgical lights bleach out reticular veins and some telangiectasias.

HAND POSITION

A syringe of sclerosant is prepared with a 30-gauge needle that has been bent to an angle of 10 to 30 degrees with the bevel up. The needle is placed flat on the skin so that the needle is parallel to the skin surface. The nondominant hand plays an important role in stabilization of the syringe. The injecting hand rests on the patient's leg with the fourth and fifth finger providing stabilization in a fixed position to facilitate controlled penetration of the vessel. The nondominant hand is used to stretch the skin around the

needle and may offer additional support for the syringe. The firmly supported needle is then moved slowly 1 to 2 mm forward, piercing the top of the tiny vein just sufficiently to allow infusion of solution with the most minimal pressure on the plunger.

A

B

FIGURE 14.4 Use of cross-polarized lighting to increase visualization of telangiectasias. **A**. Thigh telangiectasias as seen with conventional light. **B**. Group of telangiectasias in center of thigh as visualized using cross polarized light (InVu Vantage, Syris Scientific, Grey, ME).

CANNULATION OF THE VESSEL

The technique requires a gentle, precise touch, but with practice the beveled tip of the 30 gauge (0.3 mm diameter) needle may be used to cannulate vessels as small as 0.1 mm. The bevel of the needle usually can be seen within the lumen of the telangiectasias with use of 1.75 to 2× magnification. Needles smaller than 30 gauge or longer than one-half inch are difficult to use because they tend to veer off course when advanced through the skin. Depending on the patient's skin type, needles can become dull rather quickly, and should be replaced whenever resistance to skin puncture is noted. This typically occurs within three to 10 punctures. In the United States, one must follow OSHA blood-borne pathogen guidelines when changing needles.

Once the needle tip is seen in the lumen of the vessel, a tiny bolus of air (<0.05 cc) may be injected to help demonstrate that the needle is within the vein. With the use of glycerine as a sclerosant we often utilize an air block technique, in which a small bolus of air (0.1 cc) is used to clear the arborizing vessels of blood before the sclerosing solution is infused. This is much smaller than previously described.[7]

INJECTION OF SCLEROSANTS

Concentrations of sclerosants used for telangiectasias are less than those used for reticular veins. Typically the solutions are not foamed. We now prefer to use 72% glycerine for the telangiectasias of a telangiectatic web-reticular vein complex (see Table 14.1). When sclerosing solutions are injected into telangiectasia, blood usually is flushed out of the vessel ahead of the solution, thus the sclerosant usually is not diluted at all. For this reason, the initial treatment of telangiectatic webs begins with the minimal effective concentration of sclerosant.[8] At the next visit, the same concentration is used if sclerosis was effective, and a higher concentration is used if sclerosis was ineffective.

The injection of telangiectasias is performed very slowly, with minimal pressure on the syringe. A few drops of sclerosant are sufficient to fill the vein and maintain contact with the vessel wall for 10 to 15 seconds. The amount infused is approximately 0.1 cc to 0.2 cc per site, and this often is suf-

TABLE 14.1 Sclerosant Concentrations for Telangiectasia and Reticular Veins

Size of vessel	Minimum effective concentration	Max concentration	Foamed	Sclerosant
Reticular 1–3 mm	0.1%	0.25%	Yes	Sodium tetradecyl sulfate (STS)
Reticular 1–3 mm	0.25%	0.5%	Yes	Polidocanol (Laureth-9)
Telangiectasias 0.2–1 mm	0.2%	0.5%	No	Polidocanol (Laureth-9)
Telangiectasias 0.2–1 mm	0.1%	0.2%	No	STS
Telangiectasias 0.2–1 mm	72% in water	Same	No	Glycerine 72%
Telangiectasias 0.2–1 mm	10% hypertonic saline and 25% dextrose	Same	No	Sclerodex™

ficient to produce blanching in a radius of 2 cm from the site of injection. Rapid flushing of the vessels with larger volumes of sclerosant or with higher pressures leads to problems with extravasation, tissue necrosis, and ulceration, as well as an increased incidence of telangiectatic matting and of hyperpigmentation.[9,10]

For glycerine injection, the telangiectasia are filled with solution and the injection is stopped. Glycerine has the least risk of causing subsequent matting or pigmentation.[11] When detergent sclerosants are used, small volumes and small areas of short duration blanching are still important to minimize side effects such as telangiectatic matting. Sometimes there is no blanching at the site of injection, but the sclerosing solution flows easily through the telangiectasia or can even be seen flowing through adjacent telangiectasias or reticular veins several centimeters away from the injection site. In this case the injection is stopped after no more than 0.5 cc of sclerosant has been injected. Immediately after injection, the treated area is gently massaged in the desired direction of further spread of sclerosant. We strongly recommend against the use of hypertonic saline as it is painful and highly ulcerogenic.

To minimize skin necrosis, extravasation must be avoided, although the risks are minimized with glycerine or very low doses of liquid 0.1% STS.[12] If there is resistance to the flow of sclerosant, or if a bleb begins to form at the injection site, the injection must be stopped immediately. Extravasation of low concentrations of polidocanol does not cause tissue necrosis, but significant extravasation of higher concentration (>0.1%) sodium tetradecyl sulfate or of hypertonic saline will cause necrosis and ulceration.[13] A randomized study in animals found the incidence of ulceration to be greater when attempts were made to dilute the extravasated sclerosant by the injection of normal saline into the area.[14] Vigorous massage of any blebs is recommended to minimize the chance of necrosis. Application of 2% nitroglycerine paste if bone white blanching is observed is applied to cause immediate vasodilatation and minimize risks of small areas of necrosis.

COMPRESSION

Compression will speed vessel clearance and reduce staining from any vessel that protrudes above the surface of the skin. After treatment of telangiectasias, compression is provided by ready-to-wear gradient compression hose (15–20 mm Hg) placed over cotton balls secured with tape at the sites of injection. If larger reticular veins (>3 mm) are treated at the same session, then compression consists of Class I 20–30 mm Hg compression. Some authorities recommend that continuous compression be applied for as long as the patient will tolerate it (usually 1–3 days). Then the stockings are removed and the cotton balls discarded; the patient bathes and reapplies his or her stockings, wearing them for the next two weeks except when bathing and sleeping. We have the patient remove both stockings and cotton balls at bedtime of the day of treatment. Compression hose are then worn daily for two weeks except when bathing and sleeping. Patients are encouraged to walk, and the only restrictions on activity are those such as heavy weightlifting that result in sustained forceful muscular contraction and venous pressure elevation.

TREATMENT INTERVALS

Physician and patient preferences play a large role in determining treatment intervals. New areas may be treated at any time, but retreatment of the same areas should be deferred for several weeks, because the immediate posttreatment appearance of telangiectasias is either bruising, matting, or pigmentation; this will ultimately clear after two to four weeks. Patients often are anxious to speed their course of treatment, but allowing a longer time between treatment sessions may minimize the number of sessions needed. We strongly recommend waiting as long as four to eight weeks between treatments.

The number of treatments needed depends on the extent of the problem and the extent of areas treated at each session. Some patients are highly responsive to treatment and can be treated with weak sclerosants in only a few sessions. Others are highly resistant and may require more sessions and stronger sclerosants. The younger the patient the better and faster the response.

After the initial series of treatments, a rest period of four to six months will allow time for pigmentation and matting to clear, and for any remaining reticular veins to establish new routes of reflux or drainage. Approximately 80% of patients will clear to their satisfaction during the first course of treatment. Any remaining telangiectatic webs or new telangiectasias are then reassessed to determine the best approach for another round of treatment.

POOR RESPONSE TO TREATMENT

When patients have had a poor response to the initial series of treatments, the original diagnosis must always be called into question. Unsuspected sources of reflux can include truncal varices, incompetent perforating veins, and unrecognized reticular vessels. If no untreated source of reflux can be identified, the patient must be carefully questioned about proper compliance with compression. Many patients abandon compression immediately after sclerotherapy, and this can lead to treatment failures. The concentration and volume of sclerosant used should also be reexamined. It is not uncommon to find that the concentra-

tions selected were ineffective for the size and type of vessel being treated.

SUMMARY

When based upon a correct diagnosis and an appropriate treatment plan, sclerotherapy is a highly effective method of treatment for telangiectasias. Formulating an effective treatment plan requires a detailed knowledge of venous anatomy, a thorough understanding of the principles and patterns of reflux, and intimate familiarity with a range of volumes and concentrations of sclerosing solutions. The results obtained depend greatly on the experience of the clinician, but with care and with attention to detail, clearing rates of 90% can be achieved in most patients. Sufficient time must be allowed between treatments.

Patient satisfaction is enhanced through education and informed consent, photographic documentation, and a measured approach to treatment. When the basic principles of diagnosis and treatment are followed meticulously, a successful outcome is highly likely. It is important to educate the patient that telangiectasias may be a lifelong problem. Development of new veins within a few years after successful treatment does not constitute treatment failure; rather, it demonstrates the chronicity of venous insufficiency.

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CHAPTER

15

Complications and Adverse Sequelae of Sclerotherapy

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This chapter is modified from: Complications and adverse sequelae of sclerotherapy. In: Sclerotherapy treatment of varicose and telangiectatic leg veins, 4e. Goldman MP, Bergan JB, Guex JJ, Eds. London: Elsevier. 2006.

As with any therapeutic technique, sclerotherapy is associated with a number of potential adverse sequelae and complications. Fairly common, and often self-limiting, side effects include cutaneous pigmentation and a flare of new telangiectasia. Relatively rare complications include localized cutaneous necrosis and systemic allergic reactions. This chapter addresses the pathophysiology of these reactions, methods for decreasing their incidence, and treatment of their occurrence.

POSTSCLEROTHERAPY HYPERPIGMENTATION

Cutaneous pigmentation to some degree is a relatively common occurrence after sclerotherapy with any sclerosing solution. It has been reported in 11% to 80%[1–3] of patients. The true incidence of hyperpigmentation is a result of many factors, including treatment technique, sclerosing solution, and concentration, as well as how the authors define pigmentation. The definition of *pigmentation* should be, "any brown-black staining of the skin occurring after sclerotherapy," with *persistent pigmentation* being separated out to those patients whose brown staining is present after one year.

Pigmentation usually is temporary. Physicians report a 1% to 2% incidence of pigmentation persisting after one year.[4–6] Pigmentation usually is linear along the course of the treated blood vessel. We use the term ghost of the blood vessel to explain to patients that it represents a resolving and not functioning vessel (see Figure 15.1).

Etiologic Factors

The cause of this pigmentation most likely results from a combination of postinflammatory hyperpigmentation (incontinence of melanin pigment) and hemosiderin deposition. However, histologic examination has demonstrated that this pigmentation is caused only by hemosiderin staining of the dermis, irrespective of the type of sclerosing solution used, pigmentation of the patient, or length of time after injection[7,8] (see Figure 15.2).

Perivascular phagocytosis of RBCs occurs either by intact cells or piecemeal after fragmentation by macrophages.[9] The intracellular fragments in the macrophage cytoplasm are further compartmentalized into hemoglobin-containing globules. Since hemosiderin is an indigestible residue of hemoglobin degradation, it may appear as aggregates up to 100 μm in diameter.[10] Hemosiderin has a variable concentration of these aggregates. Its elimination from the area through phagocytosis may take years, if it ever occurs.

The incidence of pigmentation apparently is related to multiple factors, including (1) sclerosing solution type and concentration, (2) sclerotherapy technique, (3) gravitational and other intravascular pressures, (4) innate tendency toward cutaneous pigmentation (total body iron stores and/or altered iron transport and storage mechanisms, innate enhanced histamine release or hypersensitivity, and vessel fragility), (5) postsclerotherapy treatment (graduated compression), (6) vessel diameter, and (7) concomitant medication.

Solution Type and Concentration

The extent of endothelial destruction with resulting inflammation and extravasation of RBCs is thought to influence the development of postsclerotherapy hyper-

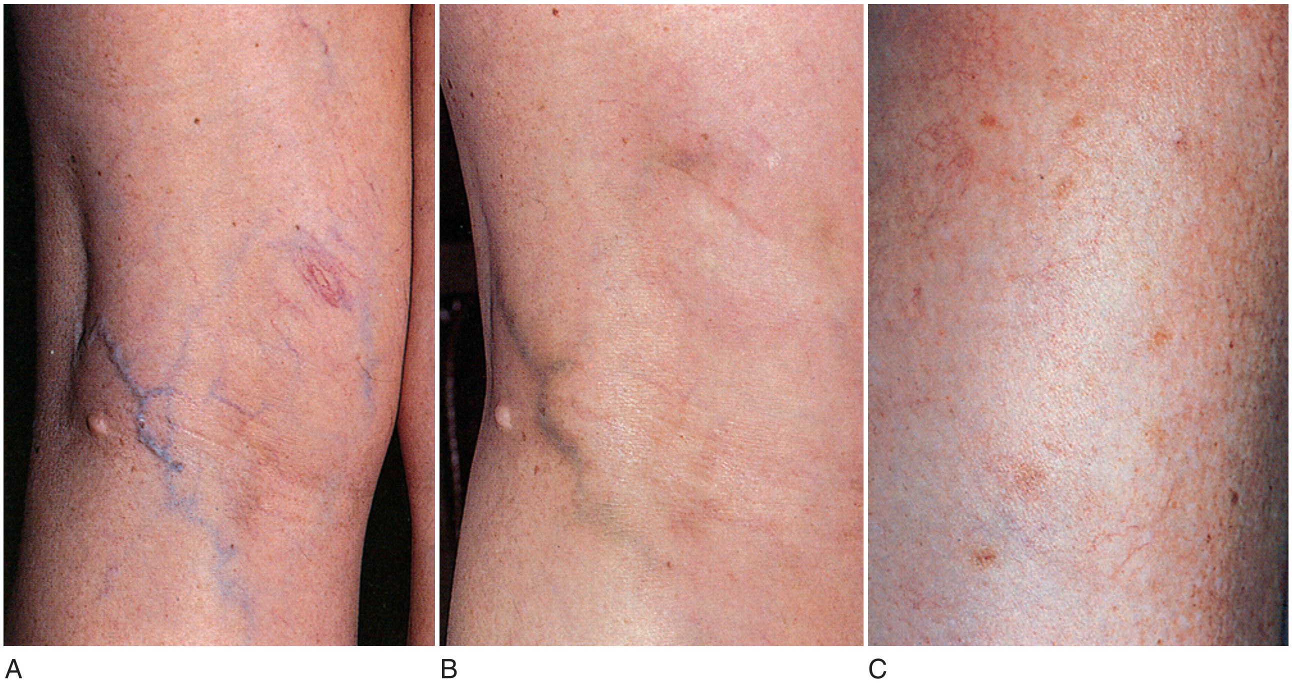


FIGURE 15.1 Linear pigmentation along the course of a treated blood vessel. **A**. Before treatment. **B**. Eight weeks after treatment with POL 0.5%. **C**. Punctate pigmentation 8 weeks after treatment with Sclerodex. (From Goldman MP. Adverse sequelae of sclerotherapy treatment of varicose and telangiectatic leg veins. In Bergan JJ, Goldman MP, eds. Varicose veins: Diagnosis and treatment. 1993, St Louis: Quality Medical Publishing.)

pigmentation. The increased incidence of pigmentation with certain concentrations of sodium tetradecyl sulfate (STS) and hypertonic saline (HS) that produce a greater reaction than polidocanol (POL) and glycerin confirms this hypothesis.[1,11,12] Thus the inflammatory response after treatment should be kept to a minimum, and sclerosing solutions and concentrations should be altered for each treatment session so that the minimally effective sclerosing concentration is used.

Technique

Optimal technique consists of limiting pressure into damaged (sclerosed) veins to prevent extravasation of RBCs. To limit the degree of intravascular pressure, larger feeding varices, incompetent varices, and points of high pressure reflux should be treated first. A greater incidence of pigmentation occurs if vessels distal to points of reflux such as reticular veins feeding into telangiectasia or vessels distal to the saphenofemoral junction (SFJ) are treated before successful closure of the junction or feeding veins.[13]

The degree of injection pressure is also important. Because telangiectasia and small venules are composed essentially of endothelial cells with a thin (if any) muscular coat and basement membrane, excessive intravascular pressure from injection may cause vessel rupture. In addition, endothelial pores and spaces between cells in the vascular wall dilate in response to pressure, leading to extravasation of RBCs. It is therefore important to inject intravascularly with minimal pressure. Since injection pressure is inversely proportional to the square of the piston radius, a syringe with a larger radius causes less pressure. The average piston radius is 8 mm for a 2-ml syringe and 5 mm for a 1-ml syringe. The calculated pressure with an implied force of 250 g is 180 mm Hg for a 2-ml syringe and more than 300 mm Hg for a 1-ml syringe.[14] This is one reason we recommend using a 3-ml syringe for sclerotherapy.

Gravitational and Other Intravascular Pressures

Postsclerotherapy pigmentation appears most commonly in vessels treated below the knee but can occur anywhere on the leg, probably as a result of a combination of increased capillary fragility and increased intravascular pressure by gravitational effects in this location. Pigmentation has never been observed in our practice after sclerotherapy on the hands, face, or chest.

Predisposition to Pigmentation

Certain individuals appear to be predisposed to the development of pigmentation through a variety of genetic mechanisms. Vessel fragility may also result in an innate predisposition toward pigmentation.

Patients taking minocycline may have an increased risk for postsclerotherapy pigmentation.[15] This propensity may

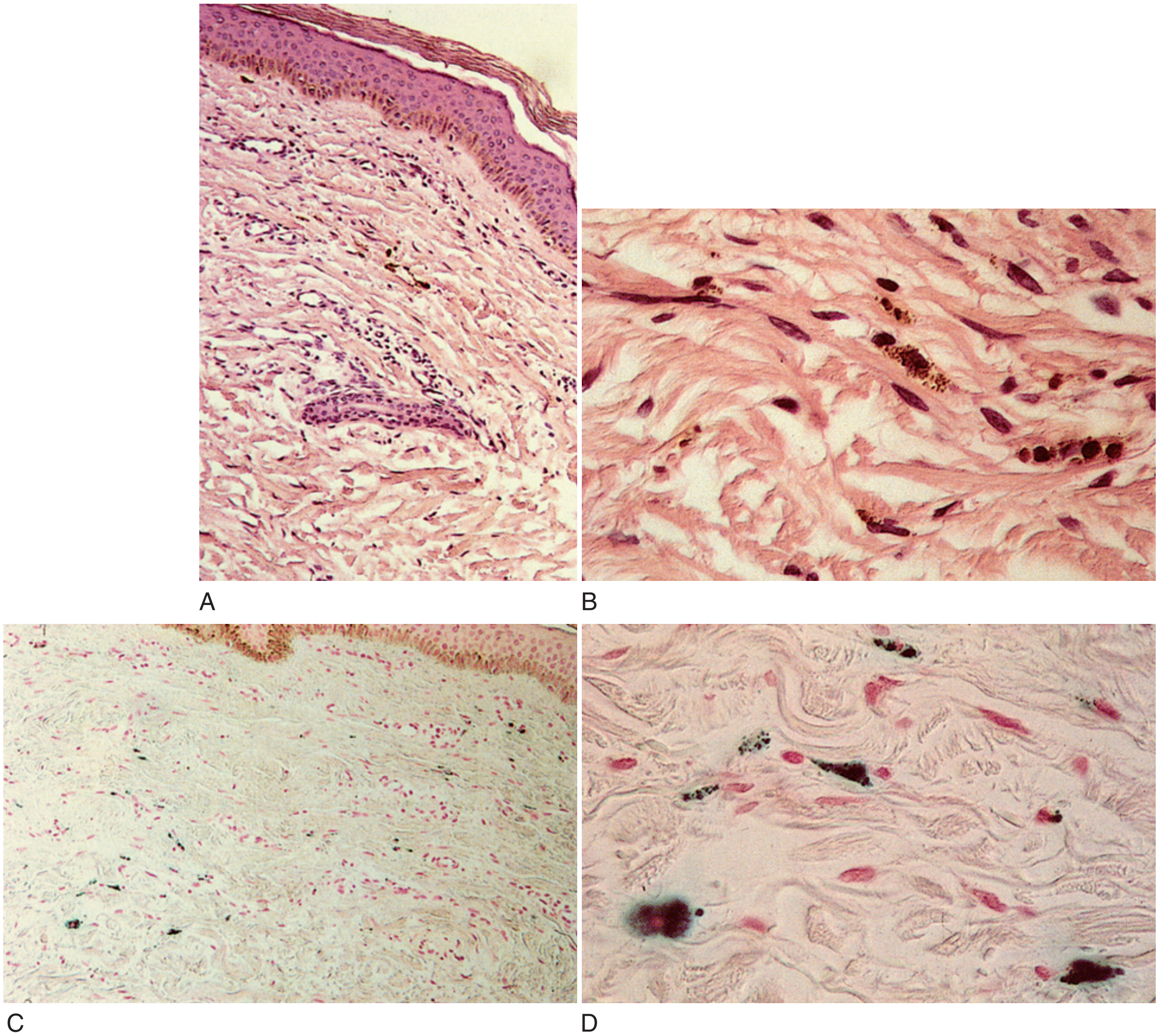


FIGURE 15.2 Section stained with hematoxylin-eosin taken 6 months after injection with POL 0.75%. Note scattered foci of golden brown pigment. **A**. Original magnification ×50. **B**. Perls-stained section from the same patient as in Figure 15.1. Note scattered foci of green-blue granules within siderophages. Original magnification ×200. **C**. Original magnification ×50. **D**. Original magnification × 350. (From Goldman MP, Kaplan RP, and Duffy DM. J Dermatol Surg Oncol 13:547. 1987.)

be related to the inflammatory effects of sclerotherapy. Unlike the golden to deep brown color characteristic of typical sclerotherapy-induced pigmentation, pigmentation from minocycline is typically blue-gray. Therefore it may be prudent to withhold minocycline therapy in sclerotherapy patients.

Postsclerotherapy Coagula

Removal of postsclerotherapy coagula may decrease the incidence of pigmentation. Thrombi to some degree are thought to occur after sclerotherapy of all veins, regardless of size, because of the inability to occlude the vascular lumen completely with external pressure. Persistent thrombi are thought to produce a subacute "perivenulitis" that can persist for months.[16] The perivenulitis favors extravasation of RBCs through a damaged endothelium or by an increase of the permeability of treated endothelium. This provides a rationale for drainage of all foci of trapped blood two to four weeks after sclerotherapy. Sometimes blood can be released even two months after sclerotherapy.

Thrombi are best removed by gentle expression of the liquefied clot through a small incision made with a 21-gauge needle (see Figure 15.3). A multicentered, randomized controlled study of 101 patients with varicose veins was treated at one to three weeks with microthrombectomy in half of

A

B

FIGURE 15.3 Method for evacuation of a thrombosis in a 1 mm diameter reticular varicose vein 2 weeks after sclerotherapy. **A**. Small incision. **B**. Expelling clot (see text for details). (From Complications of Sclerotherapy. In Sclerotherapy Treatment of Varicose and Telangiectatic Leg Veins, 4e. Goldman MP, Bergan JB, Guex JJ, eds. London: Elsevier. 2006.)

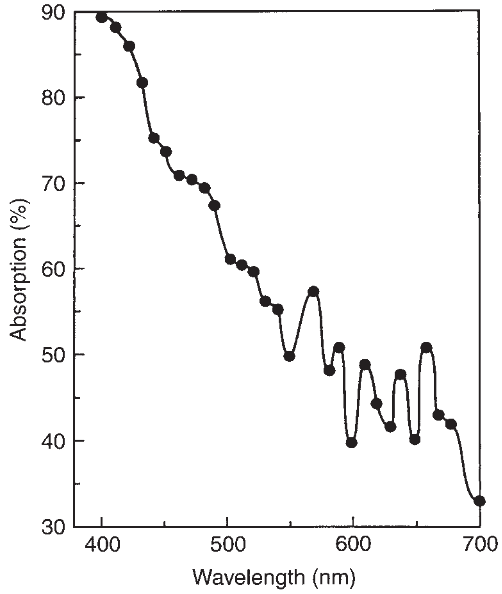


FIGURE 15.4 Absorption spectra for hemosiderin (freshly frozen, average of two determinations). (From Wells CI, Wolken JJ. Biochemistry: microspectophotomotry of haemosiderin granules, Nature. 1962. 193:977.)

the treated veins.[17] Photographs of the sclerotherapy treated areas were evaluated at 16 weeks. Veins < 1 mm in diameter had less pigmentation when drained but veins > 3 mm did not show any benefit from microthrombectomy.

Treatment

Treatment of pigmentation, once it occurs, often is unsuccessful unless you have access to a Q-switched laser. Because this pigmentation is caused primarily by hemosiderin deposition and not melanin incontinence, bleaching agents that affect melanocytic function usually are ineffective. Exfoliants (trichloroacetic acid) may hasten the apparent resolution of this pigmentation by decreasing the overlying cutaneous pigmentation or promoting the exfoliation of hemosiderin, but they carry a risk of scarring, permanent hypopigmentation, and postinflammatory hyperpigmentation.

It seems reasonable to promote the wearing of graduated support stockings after treatment. A study on the use of 20 to 30 mm Hg compression stockings after sclerotherapy treatment of telangiectasia and reticular veins 0.4 to 3 mm in diameter found a decreased incidence of pigmentation when compression was used. Compression for three days resulted in a 20% decrease of pigmentation; compression for one week resulted in a 60% decrease in pigmentation versus no compression and compression for three weeks demonstrated limited pigmentation in only two of 10 patients.[18] This follows the logic of compression reducing vessel lumen size, resulting coagula, and reducing hydrostatic pressure.

The Q-switched ruby laser (694 nm) is effective in removing recalcitrant pigmentation.[19] Hemosiderin has a peak at 694 nm, and the Q-switching impulse at 20 to 30 nsec is effective in removing tattoo granules. In addition, 694 nm is not absorbed to a significant extent by epidermal melanin or hemoglobin and thus has a relative specificity for dermal hemosiderin (see Figure 15.4). In a study of eight patients with pigmentation present one to two years after sclerotherapy, 92% of the lesions lightened with treatment; 58% of lesions demonstrated significant (75% to 100%) resolution after one to three (average 1.7) treatments. The ruby laser was used with a 4 mm beam size, and fluence range of 5.6 to 10.5 J/cm^2. We now use a Q-switched ruby laser (Sinon) from WaveLight Laser Technologies AG (Erlangen, Germany) at 5-7 J/cm^2 with a 20-ns pulse and 4 to 5 mm diameter spot size. Treatments are performed every four weeks until resolution. Care is taken to use the minimal fluence required to produce a whitening of the skin without

A B

FIGURE 15.5 **A**. Resolution 2 months after the second of two treatments with the Q-switched ruby laser at 8.0 J/cm^2. **B**. Pigmentation from sclerotherapy lasting over 1 year. (Courtesy David Duffy, MD; from Goldman MP, Weiss RA, Bergan JJ, eds. Varicose veins and telangiectasias: Diagnosis and treatment. 1999. St Louis: Quality Medical Publishing.)

causing bleeding. Our patients require one to two treatments for complete resolution (see Figure 15.5).

Interestingly, we have not found satisfactory results using a variety of Alexandrite lasers either in long pulse or Q-switched mode. This may be due the decreased interaction of the 755-nm wavelength with hemosiderin.

The simplest treatment is flashbulb therapy or chromotherapy. Since pigmentation usually resolves within one year in the majority of patients, time and photographic documentation to demonstrate resolution are usually all that is necessary for the understanding patient.

TELANGIECTATIC MATTING

The new appearance of previously unnoticed, fine red telangiectasia occurs in a number of patients. The reported incidence varies from 5% to 75%.

Reasons for the development of TM are multiple. Recovery from an ischemic injury such as closing blood vessels with sclerotherapy may produce a hypoxia-induced neovascularization. In addition, injury to endothelial cells may stimulate the release of a variety of growth factors. These responses are probably a fundamental feedback response, acting to satisfy tissue needs for oxygenation. For example, this response commonly is seen in myocardial collateralization. Given these protective factors, it is curious that the incidence of TM after sclerotherapy is not higher; therefore other innate factors must predispose to the development of TM.

Although most authors do not comment on a sexual predisposition, we have seen the development of TM in only one male patient with leg telangiectasia. Because fewer men seek treatment for leg telangiectasia than women, an accurate appraisal of the sexual incidence of TM cannot be stated.

TM may appear anywhere on the leg and we have never seen it to occur on the face, hand, or chest after sclerotherapy treatment. Duffy has reported that in 80% of his patients TM developed within 10 inches of the knees (personal communication, Oct 1994). Our experience is similar to Duffy's. Duffy postulates that relative ischemia occurs in this area from tissue hypoxia that results from the thighs and knees pressing on each other during sleep when one lies on his or her side. Hypoxia has been found both in the retina and around compressive tumors to promote vascular endothelial growth.

Probable risk factors for the development of TM in patients with leg telangiectasia include obesity, use of estrogen-containing hormones, pregnancy, and a family history of telangiectatic veins. Excessive postsclerotherapy inflammation also may predispose toward development of TM.

After sclerotherapy, the development of TM occurs rapidly, often patients report the development over a few

days three to six weeks after treatment. Normally, the more than one trillion endothelial cells that line blood vessels have a turnover time of more than 1000 days.[20] However, under appropriate conditions new vessels can develop in two to three days. Observations of mammalian systems have demonstrated the development of a vein from a capillary, an artery from a vein, a vein from an artery, or from either back to a capillary. In coronary vessels the number of arterioles and capillaries increases within one week after injury.

A study comparing different times of postsclerotherapy compression in treating leg telangiectasia also demonstrated a decrease in TM when compression was maintained for one to three weeks (5%) versus three days (30%) or no compression (40%).[21] This is most likely a reflection of a decrease in intravascular thrombosis with prolonged graduated compression, which results in a decreased phlebitic effect with decreased inflammation.

Estrogen may play a role in the development of TM. It appears that the incidence of persistent TM may be increased in patients taking systemic estrogen preparations. Weiss and Weiss[22] found a relative risk of 3.17 ($p > 0.003$) for development of TM while patients were receiving exogenous estrogen. The mechanism for promotion of TM by estrogen is speculative but may be the result of its effect on modulating mast cell responses.

In addition, Davis and Duffy[23] have reported on the virtual disappearance of leg telangiectasia and TM in a 51-year-old woman with estrogen-receptor–positive breast carcinoma after initiation of antiestrogen therapy with tamoxifen citrate (Nolvadex). This may be due to the inhibition of angiogenesis by tamoxifen.

Prevention and Treatment

Regardless of the cause of TM, since patients seek treatment to eliminate leg telangiectasia, it is disconcerting for the sclerotherapist to produce new areas of telangiectasia. Unfortunately, despite one's best efforts, TM occurs in a significant percentage of patients. Fortunately, TM usually resolves spontaneously over three to 12 months. Our experience is that less than 1% of patients will have TM persisting for one year (see Figure 15.6).

Treatment methods for TM are limited. Reinjection with hypertonic solutions or glycerin may be helpful. Because of the extremely small diameter of these vessels, use of a 31–33-gauge needle is helpful. Injection of any feeding reticular veins or venulectases into the TM area also should occur.

Various vascular-specific lasers and intense pulsed light (IPL) sources may be useful in treating these vessels.[24] In our practice, at least 75% of patients with persistent TM partially or completely improve after laser or IPL treatment. Interestingly, individual TM lesions may respond better to one laser or IPL than another. Reasons for the variable response are speculative. The 532-nm long-pulse Nd:YAG laser set at the highest fluence and pulse durations available has been found to be most effective on the most recalcitrant lesions. However, persistent and rarely permanent hypopigmentation may occur. The use of the PDL may also be effective but result in long-term hyperpigmentation. Unfortunately, even with all these therapeutic approaches, rare TM may be resistant to treatment, possibly because these resistant TM lesions may have a feeding arteriolar network that prevents persistent vessel elimination.

CUTANEOUS NECROSIS

Etiology

Cutaneous necrosis may occur with the injection of any sclerosing agent even under ideal circumstances and does not necessarily represent physician error. Fortunately, its occurrence is rare. Its cause may be the result of (1) extravasation of a sclerosing solution into the perivascular tissues, (2) injection into a dermal arteriole or an arteriole feeding into a telangiectatic or varicose vein, (3) a reactive vasospasm of the vessel, or (4) excessive cutaneous pressure created by compression techniques.

Extravasation

Extravasation of caustic sclerosing solutions may directly destroy tissue. The extent of tissue injury is related directly to both the concentration of the sclerosing solution and the quantity extravasated. As discussed later, different sclerosing solutions have a greater or lesser ability to destroy tissue. Since the final clinical appearance of the skin may not be apparent for several days, therapeutic intervention must be undertaken as soon as possible in all cases.

Clinically, bright erythema is present in the skin overlying the extravasated solution. With certain extravasation injuries, the formation of epidermal blistering may occur but does not predict a partial-thickness injury, although it may precede eventual full-thickness necrosis.

During injection of an abnormal vein or telangiectasia, even the most adept physician may inadvertently inject a small quantity of sclerosing solution into the perivascular tissue. A tiny amount of sclerosing solution may be left in the tissue when the needle is withdrawn, and sclerosing solution may leak out of the injected vessel, which has been traumatized by multiple or through-and-through needle punctures. Rarely the injection of a strong sclerosing solution into a fragile vessel may lead to endothelial necrosis and rupture, producing a "blow-out" of the vessel and perivascular extravasation of sclerosing solution. Therefore injection technique is an important but not foolproof factor in avoiding this complication even under optimal circumstances.

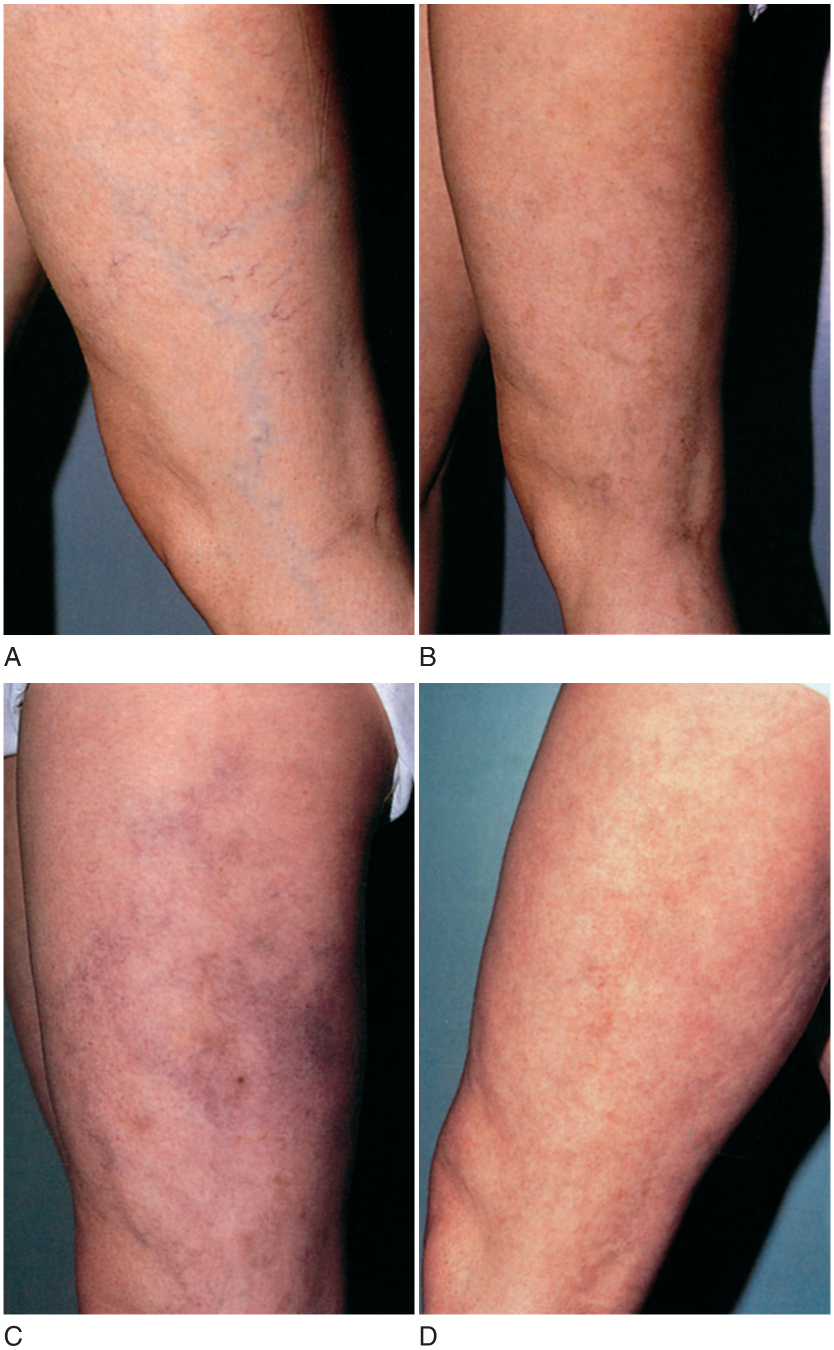


FIGURE 15.6 Typical telangiectatic matting (TM) in a 36-year-old woman. **A**. Left lateral thigh before sclerotherapy treatment. **B**. Three months after treatment of reticular veins with POL 0.75%. **C**. Six weeks after treatment of telangiectatic veins with POL 0.5%; note development of extensive TM. **D**. Six weeks later; note complete resolution of TM without treatment. (From Goldman MP. Adverse sequelae of sclerotherapy treatment of varicose and telangiectatic leg veins. In Bergan JJ, Goldman MP, eds. Varicose veins: Diagnosis and treatment. 1993. St Louis: Quality Medical Publishing.)

Hyperosmotic agents with an osmolality greater than that of serum (281 to 289 mOsm/L) can cause tissue damage as a result of osmotic factors. Epidermal necrosis even has occurred from extravasation of solutions containing 10% dextrose.[25] HS 23.4% is a caustic sclerosing agent as demonstrated in intradermal injection experiments. Clinically, small punctate spots of superficial epidermal damage occur at points of injection, especially when a small bleb of the solution escapes from the vein. However, subcutaneous injection of up to 1 ml of HS 23.4% (by mistake) in lieu of

lidocaine into the neck or cheek has been reported to result in no adverse sequelae. However, the increasing frequency of cutaneous necrosis occurring after extravasation of inadvertent subcutaneous injection of HS has moved the Department of Health and Human Services and the product manufacturer (American Regent Laboratories, Inc.) to recommend that HS be stored only in pharmacies where all dilutions would be performed before dispensing. This would eliminate the possibility of an iatrogenic medication error outside the pharmacy (Mary Helenek, American Regent Laboratories, Inc., written communication, May 1990).

Experimentally, POL apparently is minimally toxic to subcutaneous tissue. Duffy[26] has reported injecting 0.5 ml of a 3% solution of POL directly into his own forearm skin without the development of an ulceration. POL in sufficient concentration causes cutaneous necrosis. Solutions of POL greater than 1.0% may produce superficial necrosis with intradermal injection. This unfortunately occurred with the mistaken injection of 0.1 ml POL 5% solution into a leg telangiectasia 0.2 mm in diameter in our practice. This injection resulted in extensive overlying cutaneous necrosis that took eight weeks to heal. Therefore POL is not without the risk of cutaneous necrosis if a strong enough concentration is injected.

Although STS is more toxic to tissue than POL, with extravasation, concentrations above 0.25% usually are necessary to produce ulceration. Banning reported on the development of ulcerations in five of 4860 consecutive patients after telangiectasia were injected with STS 0.1% (presentation at the eighth annual meeting of the North American Society of Phlebology, Ft. Lauderdale, Fla, February 28, 1995). As discussed later, this probably represents injection into an arteriole.

Glycerin or chromated glycerin (CG) solutions have not been reported to produce cutaneous necrosis with extravasation. Duffy (personal communication, 1992) has shown that injection of full-strength CG will not produce cutaneous necrosis when it is injected into the mid-dermis. Histologic examination of his patient showed no evidence of dermal or epidermal damage.

Even when sclerotherapy is performed with expert technique, using the safest sclerosing solutions and concentrations, cutaneous ulceration may occur. Therefore it appears that extravasation of caustic sclerosing solutions alone is not totally responsible for this complication.

Arteriolar Injection

De Faria and Moraes[27] have observed that one in 26 leg telangiectasias is associated with a dermal arteriole. Bihari and Magyar[28] have found pulsatile flow in 68.9% of patients in 16 of 18 biopsies 2.5 × 1.5 cm taken from the pulse-positive telangiectasia in patients demonstrating arteriovenous microshunts. This gives a 61% incidence of AV microshunts in patients with leg telangiectasia. An expanded study of 155 patients with leg telangiectasia demonstrated a 72.2% incidence of pulsitile flow by the same group.[29] The higher incidence found in the later two studies probably is caused by the larger biopsy specimens taken. Of the 22 Doppler-positive telangiectasia, 19 demonstrated AV microshunts on biopsy. Thus it is likely that rapid injection or large volume injection into leg telangiectasia that are associated with microshunts will force the sclerosing solution into the arterial circulation. It is our opinion that inadvertent injection into or near this communication is the most common cause of cutaneous ulcerations.

It has been shown by Duffy as well as our experience that when POL is injected intradermally to effect sclerosis of TM cutaneous ulceration does not occur, even with the injection of 0.5 ml of a 0.75% solution. However, we have noted the development of 3- to 6-mm diameter ulcerations in approximately 0.0001% of injections with POL 0.5%. Five consecutive ulcerations that appeared over the course of 12 months were excised. In these patients each cutaneous ulceration developed as the result of the occlusion of the feeding dermal arteriole. This produced a classic wedge-shaped arterial ulceration (see Figure 15.7). The Australian Polidocanol Open Clinical Trial at two years reported 43 ulcers on 32 legs after sclerotherapy treatment of varicose and telangiectatic leg veins on 12,544 legs, for an incidence of 0.23%.[30] Therefore it appears that rare cases of small ulcerations may be unavoidable to some extent.

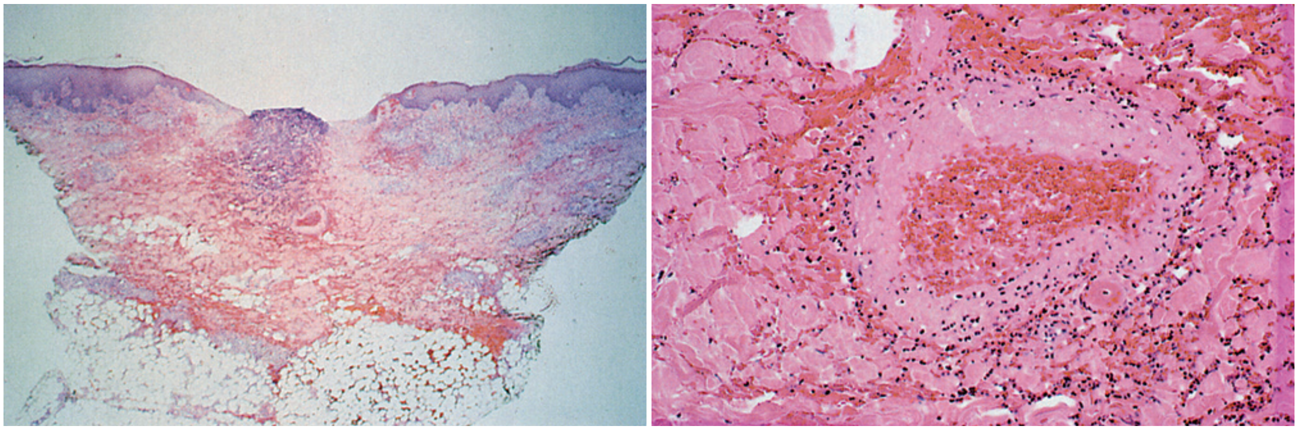
Interestingly, since we have been using glycerin solution in a 72% concentration mixed 2 : 1 with 1% lidocaine with or without epinephrine 1 : 100,000 we have not seen ulcerations at all. The safety of glycerin may be its high viscosity, which prevents the solution from flowing into arteriole connections. Alternatively, the epinephrine mixed into the solution may put the arteriolar portion of the AV anastomosis into spasm and/or the lidocaine portion may vasodilatate and protect the arteriolar portion of the AV anastomosis.

Vasospasm

Rarely after injection of the sclerosing solution an immediate porcelain-white appearance is noted at the site of injection. A hemorrhagic bulla usually forms over this area within two to 48 hours and progresses to an ulcer. This cutaneous reaction might represent an arterial spasm.

Vasospastic reactions of arteries occur in predisposed individuals for unknown reasons. This may occur even with puncture of the artery without injection of sclerosing solution. Thus small vessels, when irritated in susceptible patients, may spasm.

In an attempt to reverse the spasm, vigorous massage when the white macule appears usually prevents the devel-



A B

FIGURE 15.7 **A**. Low-power view showing skin ulceration and focal inflammation extending into the subcutaneous fat. A thrombosed vessel, most likely an artery, is present directly under the area of necrosis (hematoxylin-eosin; ×25). **B**. Higher magnification of same area as in **A**, showing a thrombosed artery that caused the infarct. The arterial lumen is completely occluded by fresh thrombus (hematoxylin-eosin; ×200). (From Complications of Sclerotherapy. In Sclerotherapy Treatment of Varicose and Telangiectatic Leg Veins, 4e. Goldman MP, Bergan JB, Guex JJ, eds. London: Elsevier. 2006.)

opment of ulceration. However, prevention of the ulceration with massage alone is not always successful. Massaging in a nitroglycerin ointment 2% is more likely to prevent the development of ulcerations in this setting. The major systemic action of nitrates is a direct reduction in venous smooth muscle tone. Nitrates also relieve spasm of angiographically normal and diseased arteries.

Arterial spasm also may explain the development of cutaneous ulceration upstream from the injection site (see Figure 15.8). In this latter case, 2 ml of POL 0.25% was injected into a feeding reticular vein (arrow, Figure 15.8). That was the only injection given to the patient in that sclerotherapy session. This also has been reported by Rabe, and was termed *embolia cutis medicamentosa*.[31]

FIGURE 15.8 Cutaneous necrosis 6 weeks after sclerotherapy with POL 0.25%. Note that 2 ml of solution was injected into a feeder vein approximately 10 cm distal to the necrotic area. (From Complications of Sclerotherapy. In Sclerotherapy Treatment of Varicose and Telangiectatic Leg Veins, 4e. Goldman MP, Bergan JB, Guex JJ, eds. London: Elsevier. 2006.)

Prevention

If extravasation of sclerosing solution occurs, the solution must be diluted as soon as possible. Hypertonic solutions should be diluted with copious amounts of normal saline solution. At least 10 times the volume of extravasated solution should be injected to limit osmotic damage.

Detergent sclerosing solutions of adequate strength also may be toxic to tissues. Dilution is again of paramount importance. Dilution with hyaluronidase in normal saline solution limits the extent and prevents development of cutaneous necrosis from 3% STS.[32] Hyaluronidase (Wydase, lyophilized, 150 USP U/ml) enzymatically breaks down connective tissue hyaluronic acid. This is hypothesized to disrupt the normal interstitial fluid barrier to allow rapid diffusion of solution through tissues, thereby increasing the effective absorption. In addition to its enhanced dilutional ability, hyaluronidase may have an independent cellular preservation function.

Hyaluronidase injection improves skin flap survival.[33] This has been postulated to occur through enhanced nutritive flow. Enhanced healing with resolution of painful induration was observed when 250 U of hyaluronidase was injected in an area where neoarsphenamine and oxophenarsine

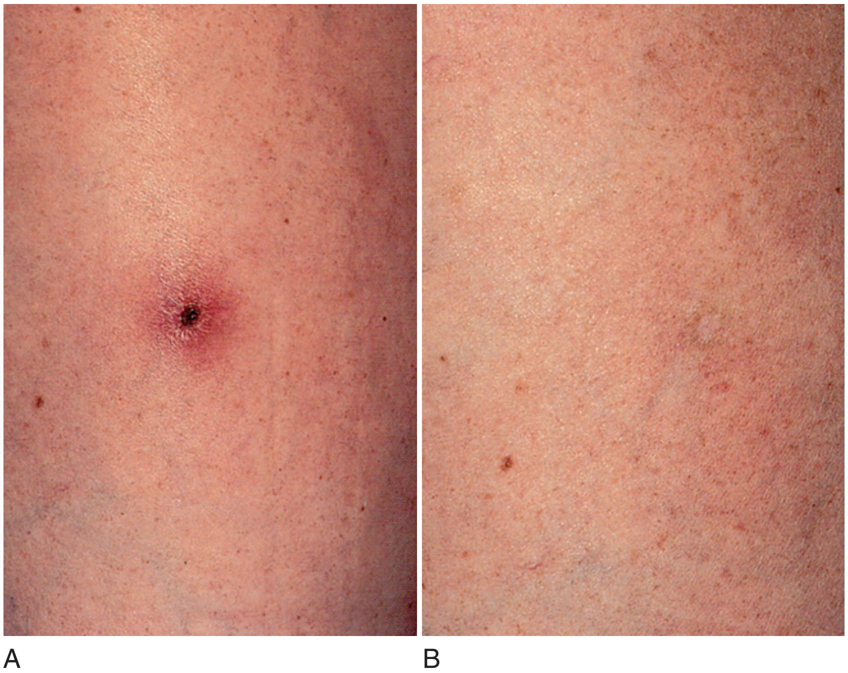


FIGURE 15.9 Cutaneous ulceration on the posterolateral thigh. **A**. Three weeks after treatment with POL 0.5%. **B**. After 6 months. Treatment consisted of a duoderm dressing that was changed every 4 days until complete healing occurred in 5 weeks. Note the cosmetically acceptable stellate scar. (From Complications of Sclerotherapy. In Sclerotherapy Treatment of Varicose and Telangiectatic Leg Veins, 4e. Goldman MP, Bergan JB, Guex JJ, eds. London: Elsevier. 2006.)

(Mapharsen) were extravasated subcutaneously.[34] Finally, hyaluronidase promotes wound repair in fetal skin, contributing to scarless repair of wounds by as yet unclear mechanisms.[35] In summary, accelerated dilution, cellular stabilization, and wound repair properties of hyaluronidase appear useful in preventing cutaneous necrosis from inadvertent sclerosing solution extravasation.

Side effects from hyaluronidase use are rare and generally of the urticarial type. Because of its limited stability, it should be reconstituted with 0.9% sodium chloride solution immediately before use. The ideal concentration and quantity to inject after extravasation have been reported to be 75 units in a volume of 3 ml. Higher doses did not appear to improve clinical outcome after intradermal infiltration of 0.25 ml of 23.4% HS.[36] For maximum effectiveness we recommend injecting the diluted solution into multiple sites around the extravasated area. Studies have demonstrated that hyaluronidase solution must be injected within 60 minutes of extravasation to be effective.[37]

Treatment

Whatever the cause of the ulceration, it must be dealt with when it occurs. Fortunately, ulcerations, when they do occur, are usually fairly small, averaging 4 mm in diameter in our practice. At this size primary healing usually leaves an acceptable scar (see Figure 15.9). In addition to various topical therapies directly applied to the ulcer, elevation of the affected extremity and systemic pentoxifylline may be helpful in minimizing the ulcer size.

Pentoxifylline may decrease tissue injury of ischemia-reperfusion by inhibiting the production of platelet-activating factor during reperfusion.[38] Pentoxifylline should improve microcirculatory dysfunction observed during reperfusion of ischemic tissues. Pentoxifylline causes increased deformability of RBCs and lowers blood viscosity.[39] The optimal dosage appears to be 25 mg/kg for protective effects in experimental studies in the canine gracilis muscle model. However, the dosage that produces maximal protective effects in humans is unknown.

We have found that the use of occlusive or hydrocolloid dressings results in an apparent decrease in wound healing time. Occlusive dressings do not speed healing of full-thickness ulcers until granulation tissue has formed. Hydrocolloid gel dressings enhance debridement of wounds, possibly through their pectin-gelatin base. Nongelatin, nonpectin hydrocolloid dressings only act to stimulate fibrin lysis. Thus its enhanced efficacy may be related to wound debridement, which always should be used either medically or surgically to promote granulation tissue formation. More important, the use of occlusive dressings decreases the pain associated with an open ulcer. Dressings must be changed

every three to four days, and necrotic tissue should be sharply debrided every week or two as needed to promote granulation tissue. However, because an ulcer may take four to six weeks to heal completely even under ideal conditions, if possible, excision and closure of these lesions are recommended at the earliest possible time. This affords the patient the fastest healing and an acceptable scar.

SYSTEMIC ALLERGIC REACTION OR TOXICITY

Systemic reactions caused by sclerotherapy treatment occur very rarely. Anaphylaxis is a systemic hypersensitivity response caused by exposure or, more commonly, reexposure to a sensitizing substance. Anaphylaxis is usually an IgE-mediated, mast cell–activated reaction that occurs most often within minutes of antigen exposure. Other classes of immunoglobulin such as IgG also may produce anaphylaxis. Since the risk of anaphylaxis increases with repeated exposures to the antigen, one should always be prepared for this reaction in every patient.

The principal manifestations of anaphylaxis occur in areas where mast cell concentrations are highest: skin, lungs, and gastrointestinal (GI) tract. Histamine release is responsible for the clinical manifestations of this reaction. Although urticaria and abdominal pain are common, the three principal manifestations of anaphylaxis are airway edema, bronchospasm, and vascular collapse. Urticaria alone does not constitute anaphylaxis and should not be treated as such because of the potential side effects of treatment with epinephrine, especially in older patients.

The signs and symptoms of anaphylaxis initially may be subtle and often include anxiety, itching, sneezing, coughing, urticaria, and angioedema. Wheezing may be accompanied by hoarseness of the voice and vomiting. Shortly after these presenting signs, breathing becomes more difficult, and the patient usually collapses from cardiovascular failure resulting from systemic vasodilation. One helpful clue in distinguishing between anaphylaxis and vasovagal reactions is heart rate. Sinus tachycardia almost always is present in a patient with anaphylaxis, whereas bradycardia or cardiac rhythm disturbances are commonplace in vasovagal reactions.

The recommended treatment is epinephrine, 0.2 to 0.5 ml 1 : 1000 subcutaneously. This can be repeated three or four times at 5- to 15-minute intervals to maintain a systolic blood pressure above 90 to 100 mm Hg. This should be followed with establishment of an IV line of 0.9% sodium chloride solution. Diphenhydramine hydrochloride, 50 mg, is given next along with cimetidine, 300 mg; both the IV solution and oxygen are given at 4 to 6 L/min. An endotracheal tube or tracheotomy is necessary for laryngeal obstruction. For asthma or wheezing, IV theophylline, 4 to 6 mg/kg, is infused over 15 minutes. At this point it is appropriate to transfer the patient to the hospital. Methylprednisolone sodium succinate, 60 mg, is given IV and repeated every six hours for four doses. Corticosteroids are not an emergency medication because their effect appears only after one to three hours. They are given to prevent the recurrence of symptoms three to eight hours after the initial event. The patient should be hospitalized overnight for observation.

Sodium Morrhuate

Although touted by the manufacturer as "the natural sclerosing agent," sodium morrhuate causes a variety of allergic reactions, ranging from mild erythema with pruritus to generalized urticaria to GI disturbances with abdominal pain and diarrhea to anaphylaxis. It has been estimated that "unfavorable reactions" from the treatment of varicose leg veins occur in 3% of patients.[40] The reason for the high number of allergic reactions with this product may be related to the inability to remove all the fish proteins present in sodium morrhuate. In fact, 20.8% of the fatty acid composition of the solution is unknown.

Many cases of anaphylaxis have occurred within a few minutes after injection or more commonly when therapy is reinstituted after a few weeks. Most of these cases occurred before 1950. Rarely, anaphylaxis has resulted in fatalities, many of which have not been reported in the medical literature. Bronchospasm developed in one patient while being treated with the twelfth injection under anesthesia. This responded readily to antihistamine and epinephrine. The patient was subsequently treated with sodium tetradecyl sulfate without an adverse reaction.[41]

Prolonged dysrhythmia requiring placement of a permanent pacemaker has been reported in two cases.[42] This complication has been attributed to a direct cardiotoxic effect of sodium morrhuate.

Ethanolamine Oleate

Ethanolamine oleate (Ethamolin) is a synthetic mixture of ethanolamine and oleic acid with an empirical formula of $C_{20}H_{41}NO_3$. The minimal lethal IV dose in rabbits is 130 mg/kg. The oleic acid component is responsible for the inflammatory action. Oleic acid also may activate coagulation in vitro by release of tissue factor and Hageman factor. Ethanolamine oleate is thought to have a lesser risk of causing allergic reactions compared with sodium morrhuate or sodium tetradecyl sulfate. However, pulmonary toxicity and allergic reactions have been associated with this sclerosing agent.

The product manufacturer has reported anaphylactic shock after injection in three cases (product information [1989] from Glaxo Pharmaceuticals, Research Triangle

Park, NC). Another case of a nearly fatal anaphylactic reaction during the fourth treatment of varicose leg veins with 1 ml of solution also has been reported.[43] In one additional case a fatal reaction occurred in a man with a known allergic disposition (product information [1989] from Glaxo Pharmaceuticals, Research Triangle Park, NC). Another episode of a fatal anaphylactic reaction occurred in a woman having her third series of injections. This represented one reaction in 200 patients from that author's practice. Generalized urticaria occurred in approximately 1 in 400 patients; this symptom responded rapidly to an antihistamine.[44]

Sodium Tetradecyl Sulfate

A synthetic detergent developed in the 1940s, STS has been used throughout the world as a sclerosing solution. A comprehensive review of the medical literature (in multiple specialties and languages) until 1987 disclosed a total of 47 cases of nonfatal allergic reactions in a review of 14,404 treated patients; this included six case reports.[45] A separate review of treatment in 187 patients with 2249 injections disclosed no evidence of allergic or systemic reactions.[46] An additional report of 5341 injections given to an unknown number of patients found "no unfavorable reaction."[47] Fegan[48] has reviewed his experience with STS in 16,000 patients. He reported 15 cases of "serum sickness, with hot, stinging pain in the skin, and an erythematous rash developing 30 to 90 minutes after injection." These patients subsequently underwent additional uneventful treatment with STS after premedication with antihistamines. In 10 additional patients, "mild anaphylaxis" developed that required treatment with an injection of epinephrine. If one were to combine only those reviews of over 1000 patients, the incidence of nonfatal allergic reactions would be approximately 0.3%.

The product manufacturer notes two fatalities associated with the use of STS, both from the sclerotherapy procedure itself and not specifically related to STS. One fatality occurred in a patient who was receiving an antiovulatory agent. Another death (fatal pulmonary embolism) was reported in a 36-year-old woman who was not taking oral contraceptives. Wyeth-Ayerst also was required to include in its product insert the deaths of two additional patients who were suspected of dying of anaphylactic shock after sclerotherapy treatment with STS (Mark Coyne, R.Ph., personal communication, Wyeth-Ayerst Pharmaceuticals, Aug 19, 1998). The company did not have details of the two cases except that one patient had a medical history of asthma. Four deaths attributed to anaphylactoid reactions were reported to the Committee on Safety of Medicines for the United Kingdom between 1963 and 1988, with 22 nonfatal allergic reactions such as urticaria noted over the same period.[49]

A fatality has been reported after a test dose of 0.5 ml of STS 0.5% was given to a 64-year-old woman.[50] An autopsy performed by the Hennipin County, Minnesota, coroner's office revealed no obvious cause of death. Subsequently, mast cell tryptase studies were performed on blood collected approximately one hour after the reaction while the patient was receiving life support. A normal tryptase level is less than 5 ng/ml; in experimental anaphylactic reactions induced in the laboratory, levels up to 80 ng/ml have been observed. In this patient the levels were extremely high at 6000 ng/ml, suggesting that an anaphylactoid reaction had caused her death. Unfortunately, tryptase levels are experimental at this time, and it is unclear how such a high level could be obtained. Therefore it is also unclear whether fatal anaphylaxis is a significant possibility with STS.

Since all reported cases of allergic reactions are of the IgE-mediated immediate hypersensitivity type, it is recommended that patients remain in or near the office for 30 minutes after sclerotherapy when STS is used. However, allergic reactions also may develop hours or days after the procedure. Therefore patients should be warned about the possibility of allergic reactions and how to obtain care should a reaction occur. In a review of 2300 patients treated over 16 years, four cases of allergic reactions were reported (0.17% incidence).[51] Reactions in this study were described as periorbital swelling in one patient and urticaria in three. All reactions were easily treated with oral antihistamines. It is of interest that French phlebologists have advocated a three-days-before and three-days-after treatment course with an antihistamine. P. Flurie noted no episodes of allergic reactions in 500 patients treated in this manner.[51]

In a two-year prospective study of 2,665 patients treated with STS by Paul Thibault,[52] there were four cases of anaphylactoid reactions (0.15%). These occurred 10 to 30 minutes after injection of 3% solution, with patients having facial flushing, urticaria, dizziness, tachycardia, shortness of breath, and finally GI symptoms of nausea, vomiting, and abdominal pain. All four patients responded well to a subcutaneous injection of 0.5 ml of 1:1000 epinephrine followed by promethazine HCL 25 to 50 mg intramuscularly. Urticaria occurred in an additional two patients (0.07%).

Between August 1985 and January 1990, 37 reports of adverse reactions to STS, of which five cases of suspected anaphylaxis and two cases of asthma induced by injection, were reported to the Drug Experience Monitoring Program of the Food and Drug Administration (FDA). One of the cases of anaphylaxis resulted in the death previously discussed. After a detailed review it is unclear to us whether anaphylaxis indeed occurred in every reported case.

The reports of the Clinical Drug Safety Surveillance Group of Wyeth-Ayerst Laboratories are compiled from voluntary reporting to the manufacturer or the FDA, or both. The following are summaries of those reports: January to

July 1991 disclosed one episode of erythema multiforme; one episode of ARDS; one episode of fever, lymphadenopathy, and rash; and three episodes of abdominal pain, nausea, vomiting, and diarrhea. The case report of erythema multiforme was reported in a woman after her thirteenth sclerotherapy treatment. Pruritus developed the morning after the last injection, with a generalized eruption beginning on the legs four days later. This was followed by fever the following day. A rapid tapering course of oral prednisone was given, with complete resolution of the rash in two weeks.

From September 1991 to November 1992 there were five reports of urticaria and one episode of ARDS. From December 1992 to September 1993 there was only one case of a maculopapular rash. In short, anaphylaxis has been reported, with rare fatal reactions. From September 1993 through October 1994 there was one case of angioedema, and generalized weakness was reported in one patient after receiving 10 ml of 3% STS. From November 1994 through January 1996 there was one case of anaphylaxis. From January 1996 through December 1996, there was one case of allergic vasculitis. From November 1997 through October 1999 there were three cases of urticaria and four cases of nonspecific hypersensitivity reactions. These reactions voluntarily reported to Wyeth-Ayerst occurred with approximately 500,000 2-ml ampoules of 1% and 3% being sold yearly within the United States. Thus the incidence of adverse reactions is rare. (All information regarding adverse reactions from Sotradecol was provided by Paul Minicozzi, Ph.D., Wyeth-Ayerst Laboratories, through yearly correspondence.)

A similar low experience with adverse reactions was reported by STD Pharmaceuticals, the manufacturers of sodium tetradecyl sulfate (correspondence from Robert Gardiner, Hereford, UK, March 15, 1995, and the Adverse Drug Reaction Information Tracking Product Analysis from the Medicines Control Agency of Great Britain). The adverse drug reaction reported in the United Kingdom between 1963 and 1993 was one nonspecific allergic reaction, two cases of anaphylactic shock, six cases of gastrointestinal disorder, two cases of bronchospasm, four patients with a nonspecific cutaneous eruption, and two patients with urticaria. This summary comprised 30 years, during which time an estimated 7,200,000 ml of STD 1% and 3% was sold within the United Kingdom.

The most common systemic reaction consists of transient low-grade fever and chills lasting up to 24 hours after treatment. This has also been noted in one of our patients. Of note is that three patients with allergic systemic reactions to monoethanolamine oleate had no evidence of allergy to STS.

Reactions can occur with any sclerosing solution that are not allergic in nature but represent the effect of the sclerosing solution on the vascular system. One such reaction is hemolysis that occurs through lysis of red blood cells that are present in the treated vein. A hemolytic reaction occurred in five patients in a series of more than 900 patients with injection of more than 8 ml of STS 3%. Like a similar reaction that occurred with ethanolamine oleate, patients were described as "feeling generally unwell and shivery, with aching in the loins and passage of red-brown urine. All rapidly recovered with bed rest and were perfectly normal the next day." Injections of less than 8 ml per treatment session did not result in this reaction.

Although the lethal dose in humans has never been reported, the IV median lethal dose (LD_{50}) in mice is 90 mg/kg.[53] In our practice, it is not uncommon for patients to be treated with up to 30 ml of 0.5% STS. We have not observed an adverse reaction from this dose of STS.

My experience in over 20 years in an estimated 20,000 patients is that no patient has developed a serious allergic reaction from the use of STS. Since STS from various sources may have a variable purity it appears possible that allergic reactions may occur from the impurities such as carbitol and not STS itself.[54] This may explain the decreased reported incidence of allergic reactions with the use of Fibrovein (STD Pharmaceuticals) as compared with Sotradecol (Wyeth-Ayerst) and/or Trombovar (Omega Laboratories, Montreal, Canada). Recently, Sotradecol has been approved for manufacture and sale by Bioniche Life Sciences, Inc. (Inverin Co. Galway, Ireland). Bioniche claims to have a different method for producing STS that does not involve distillation and thus contains no carbitol. The benefits of this "new" Sotradecol are unknown at the time of this writing.

Polidocanol

Allergic reactions to POL also are quite rare and have been reported in only four patients in a review of the world's literature up to 1987, with an estimated incidence of 0.01%.[45] However, since 1987 rare allergic reactions have been reported, including a case of nonfatal anaphylactic shock to 1 ml of POL 2% injected into a varicose vein during the fourth treatment session.

Guex[14] reported seven cases of minor general urticaria in nearly 11,000 patients treated over 12 years. These patients cleared completely in one to two days with antihistamine and topical corticosteroid therapy, with one patient requiring systemic corticosteroids. Kreussler GmbH, the product manufacturer in Germany, has documented 35 cases of suspected sensitivity from 1987 to 1993 (personal correspondence, January 1994). Of these reports, most were either vasovagal events or unproved allergic reactions. Nine patients were given repeat challenges with POL, with only three demonstrating an allergic reaction (urticaria or erythematous dermatitis). One patient died of anaphylactic

shock five minutes after injection with 1 ml despite maximal intervention. In 1994, Kreussler reported two patients with urticaria. In 1995, two additional patients were reported with urticaria, two with bronchospasm, and one with angioedema. In 1996, there were four reports of urticaria, two of anaphylactoid reactions, one with angioedema, one with pruritus, and one with contact allergy. Therefore POL is *not* free from allergy and like all sclerosing solutions, physicians must be prepared to evaluate and treat patients who have an allergic reaction to the sclerosing solution.

A detailed account of three serious cases of anaphylaxis was reported from the Netherlands.[55] These patients were anaphylactic within 15 minutes after injection of POL. Two of them received the drug for the first time. One patient, a 70-year-old woman with a complicated medical history of two heart operations, two cerebrovascular accidents, and hyperthyroidism, was successfully resuscitated after cardiac arrest. She was receiving multiple medications, including digoxin, carbimazole, captopril, furosemide, mebeverine, and acenocoumarol. She was treated without complications four previous times with POL. The second patient showed signs of ARDS after being treated with epinephrine and systemic methylprednisolone for shock. The third patient developed urticaria, dyspnea, paresthesia, headache, and chest pain with electrocardiographic (ECG) findings of cardiac ischemia. No further studies were performed on these patients.

The Australian Polidocanol Open Clinical Trial at two years, with over 8000 treated patients, reported nine local urticarial reactions and three generalized reactions, with two patients developing a rash, for a frequency of approximately 0.2%. There were no cases of anaphylaxis.[30] After an additional 8804 patients were evaluated, an additional three patients developed urticaria again without any additional significant adverse sequelae.[56] A five-year experience in 500 patients treated with POL 3% reported five cases of allergic reaction (1% incidence); one patient had nonfatal anaphylactic shock, with the other patients experiencing urticaria.[57]

Two of 689 sequential patients were reported who developed an immediate-type hypersensitivity reaction with systemic pruritus and urticaria.[58] This represented an incidence of 0.3% in their patient population and 0.91% for the "true" population. These two reactions occurred without prior exposure to POL as a sclerosing agent. Since POL is used as an emulsifying agent in preprocessed foods, patients may have been exposed previously through ingestion. Both patients responded easily to either a single dose of oral diphenhydramine, 50 mg, or 0.3 ml of subcutaneous epinephrine plus 50 mg diphenhydramine IM.

One specific case report describes a 30-year-old woman who underwent four separate sclerotherapy sessions with POL. On the fourth session, 3 ml of POL 1.5% and 12 mls of POL 0.5% were administered. The patient complained of chest heaviness and constriction, which also appeared after two of her other sessions but was not brought to the attention of the medical staff. During the fourth episode she lost consciousness and was found without a pulse or blood pressure with dilated pupils. Spontaneous respiration occurred after two to three minutes, she began to vomit and complained of headache and earache. She recovered and was discharged after 10 hours well but returned the next day with dysosmia, which lasted six weeks. Although a brain CT scan was normal the presumed cause was cerebral.[59]

The LD_{50} in rabbits at two hours is 0.2 g/kg, which is three to six times greater than the LD_{50} for procaine hydrochloride. The LD_{50} in mice is 110 mg/kg. The systemic toxicity level is similar to that of lidocaine and procaine.[60]

Chromated Glycerin

CG 72% (Scleremo) is a sclerosing solution with a very low incidence of side effects (Scleremo product information [1987]). Hypersensitivity is a very rare complication.[61] Contact sensitivity to chromium occurs in approximately 5% of the population.[62] IV potassium dichromate leads to complete desensitization in chromium-sensitized guinea pigs. This effect occurs because chromium needs to bind to skin proteins to become an effective antigen. This may be related to the necessity for epidermal Langerhans' cells to produce an allergic response, whereas T lymphocyte accessory cooperation is not optimal with IV injection and its resulting endothelial necrosis. Thus it is more common for a sclerotherapist to develop an allergic contact dermatitis to CG than it is for a patient to have an allergic reaction to IV use of CG. Indeed, Ouvry (personal communication, 1995) has developed an allergic contact dermatitis from CG injected without the use of protective gloves.

Ramalet[63] has reported seven patients who developed an allergic reaction to CG. One patient had a vasculitis, and six patients had an eczematous reaction. All allergic patients demonstrated a sensitivity to topically applied chrome.

Hematuria accompanied by urethral colic has been reported to occur transiently after injection of large doses of CG. Ocular manifestations, including blurred vision and a partial visual field loss, have been reported by a single author, with resolution in less than two hours.[64] Glycerin (or any sclerotherapy)-induced hemolysis may not be a benign event. Hemoglobin can exert direct cytotoxic, inflammatory, and pro-oxidant effects that adversely effect endothelial function.[65] Hemoglobin from destroyed red blood cells dimerizes and is rapidly bound by the serum protein haptoglobin. The haptoglobin-hemoglobin complex causes endocytosis and degradation, which can lead to a variety of adverse effects.[66]

An additional case was reported of transient hypertension and visual disturbance after the injection of 12 ml of 50% CG into spider and "feeder" leg veins in a fourth treatment

session.[67] These symptoms occurred two and a half hours after treatment and lasted more than three hours without treatment. This may have represented a retinal spasm or an ophthalmic migraine.

Although transient hemoglobinuria is common in athletes and without known long-term adverse effects, hemoglobulinemia can cause renal failure.[68] More commonly, hemoglobulinemia can cause a dose-related gastrointestinal dystonia and pain including esophageal spasm and dysphagia. Refer to an excellent recent review that details more clinical manifestations of hemoglobinemia.[69]

Since we have been using glycerin alone without chromium but mixed 2 : 1 with 1% lidocaine with or without 1 : 100,000 epinephrine we have yet to see an allergic reaction. We have also yet to see hemoglobinuria or adverse effects with the use of up to 12 ml of this glycerin mixture except for a minute or two of epinephrine-induced "rush" that can occur in rare patients who have a sensitivity to epinephrine.

Polyiodide Iodine

Polyiodide iodine (Varigloban; Sclerodine 6) is a stabilized water solution of iodide ions, sodium iodine, and benzyl alcohol. Sigg et al.[70,71] reported on their experience with over 400,000 injections with Variglobin reported an incidence of 0.13 allergic cutaneous reactions per 1000. No systemic allergic reactions were observed. Obvious contraindications to the use of Variglobin are hyperthyroidism and allergies to iodine and benzyl alcohol.

Sodium Salicylate

Saliject (Omega Laboratories, Montreal) has not been reported in a literature review to cause allergic reactions. Dr. Beverly Kemsley has reported 1 of 6000 patients who developed an anaphylactic reaction after the use of Saliject. Thirty patients developed localized erythema and urticaria that responded to the oral antihistamine terfenadine 120 mg (personal communication, 1996).

Hypertonic Saline

Alone, hypertonic saline (HS) solution shows no evidence of allergenicity or toxicity. Complications that may arise from its specific use include hypertension that may be exacerbated in predisposed patients when an excessive sodium load is given, sudden hypernatremia, central nervous system disorders, extensive hemolysis, and cortical necrosis of the kidneys (Mary Helenek, written correspondence, American Regent Laboratories, Inc., May 1990). These complications among others have led one manufacturer (American Regent Laboratories) to add to its label the warning "For IV or SC use after dilution" in bold red ink.

TABLE 15.1 Summary of Complications of Sclerosing Agents

Solution	Pigmentation	Allergic reaction	Necrosis	Pain
Sodium morrhuate	++	++	+++*	+++
Sodium tetradecyl sulfate	++	+	++*	+
Ethanolamine oleate	+	++	++*	++
Polidocanol	+	+	+*	0
Hypertonic saline	+	0	+++*	+++
Sclerodex (+0% saline 5% dextrose)	+	0	+	++
Chromated glycerin	0	+	0	++
Glycerin	0	0	0	+
Polyiodinated iodine	++	+	+++*	+++

+, Minimal; ++, moderate; +++, significant.
*Concentration dependent.

As discussed previously, hematuria can occur with any sclerosing agent. Sometimes blood appears in the urine after one or two acts of micturition and occasionally at other times throughout the day. Usually there are no other ill effects, and the hematuria resolves spontaneously. Hematuria probably occurs because of hemolysis of RBCs during sclerotherapy.

In summary, sclerotherapy with a wide variety of sclerosing solutions is a safe and effective procedure for the treatment of varicose and telangiectatic leg veins. Space does not permit a more complete discussion of other possible adverse effects. Table 15.1 summarizes the different adverse effects from a variety of available sclerosing solutions. The interested reader is referred elsewhere for a complete review of adverse effects from sclerotherapy treatment.[13]

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C H A P T E R

16

Laser Treatment of Telangiectasias and Reticular Veins

NEIL SADICK and LIAN SORHAINDO

INTRODUCTION

The incidence of prominent venulectasias and/or telangiectasias on the lower extremities occurs in up to 41% of women and 15% of men within the United States.[1] The current literature subdivides vascular pathology into superficial "spider" veins or telangiectasias, deep reticular veins, and protuberant varicosities. Etiologies include heredity, hormonal dysregulation, prolonged periods of standing, obesity, pregnancy, and aging. Although patients may present with symptoms of fatigue, aching, swelling, throbbing, and occasionally pain, patients seek treatment primarily for aesthetic concerns. With this rise in consumer demand over the past five years, there has been a subsequent increase in the utilization of lasers and intense pulsed light (IPL) sources for the treatment of lower extremity veins.

IDENTIFYING THE PROBLEM

The vasculature of the lower extremity is comprised of a complex, intertwined network of superficial and deep venous plexuses. The superficial veins, as suggested by their name, lie directly underneath the skin surface. The deep veins, in contrast, traverse the muscle of the leg. The individual flow patterns of these two networks intertwine to such a great degree that superficial spider veins may be the direct result of increased hydrostatic pressure in the deep reticular veins.

In contrast to the treatment of facial veins, the varying sizes, depths, flow patterns, and vessel thickness of leg veins make the treatment of leg veins more challenging. Presently, there is no gold standard of treatment for all leg veins, and lasers often are used as adjunctive therapy in patients undergoing phlebectomy, sclerotherapy, or vein stripping. Laser and light source technology have become particularly useful in the treatment of small spider veins or telangiectasias, and also in the setting of vessels that are sclero-resistant that may arise from prior surgical treatment as a result of telangiectatic matting or angiogenic flushing (see Box 16.1).[2] It can also be used in the treatment of large spider and reticular veins; however, sclerotherapy remains the gold standard for the treatment of these vessels. The chapter, herein, deals specifically with the laser treatment of telangiectasias and reticular veins; other modalities of treatment including sclerotherapy, ambulatory phlebectomy, and endovenous ablation are discussed elsewhere in the book.

PATIENT SELECTION: WHEN AND HOW TO CHOOSE LASER/IPL VERSUS SCLEROTHERAPY

Laser therapy is most efficacious for treating telangiectasia/venulectasia or reticular veins less than 3 mm in diameter.[3,4] As mentioned earlier, lasers have become indicated in patients with areas of neovascularization with telangiectactic matting or angiogenic flushing, with sclero-resistant/noncannulizable vessels, and who are needle-phobic. Relative contraindications to the use of laser surgery include tanned skin, pregnancy, the use of iron supplements or anti-coagulation, history of photosensitivity disorder, or hypertrophic and keloidal scarring (see Table 16.1).

BOX 16.1 Indications for Laser Therapy Treatment of Leg Veins

- Refractory noncannulable vessels
- Telangiectatic matting
- Angiogenic flushing
- Sclero-resistance
- Needle-phobic patients
- Vessels smaller than the diameter of a 30-gauge needle are present

BOX 16.2 Fundamental Properties of a Laser for Leg Veins

- Must have a wavelength proportionately better absorbed by hemoglobin than the surrounding tissue.
- Penetration should reach the full depth of the target vessel.
- Sufficient energy must be delivered to damage the vessel without damaging the overlying skin.
- Energy must be delivered over an exposure time long enough to slowly coagulate the vessel without damaging surrounding tissue.

TABLE 16.1 Comparison of the 1064 nm Nd:YAG, 810 nm Diode, and 755 nm Alexandrite Lasers for Leg Veins 0.3–3 mm in Diameter

Laser	Patients achieving 75% clearance at 3 months
1064 nm Nd:YAG	88%
810 nm diode	29%
755 nm Alexandrite	33%

TABLE 16.2 Vessel Thermal Relaxation Time

Vein diameter	Time (seconds)
0.1	0.010
0.2	0.080
0.4	0.16
0.8	0.6
1.0	1.0
2.0	8.0

Data from Eremia 2002.

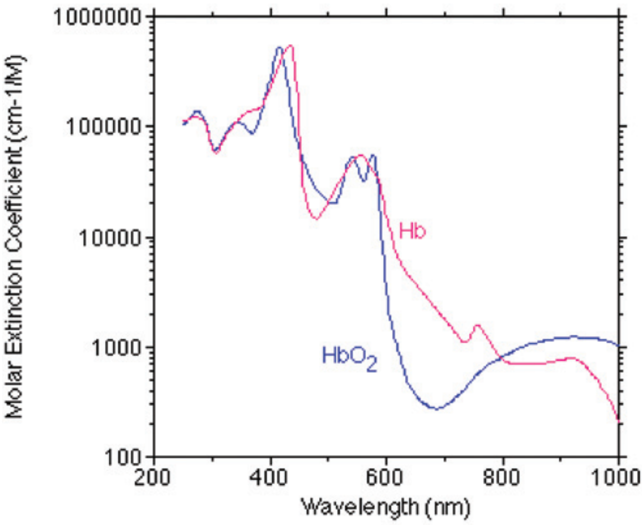

FIGURE 16.1 Absorption spectrum of hemoglobin/deoxyhemoglobin.

FUNDAMENTALS OF LASER TREATMENT OF LEG VEINS

Theory of Selective Thermolysis: Major Principles and Determinants

The advent of laser technology for treatment of leg veins began with the concept of selective photothermolysis developed in the late 1980s.[5] The theory of selective photothermolysis states that selective damage to a tissue structure is achieved by means of a wavelength of light preferentially absorbed by a chromophore in light-absorbing molecules and laser exposure time less than or equal to the object's thermal relaxation time (i.e., the time required for the object to lose 50% of its thermal energy). The thermal relaxation times of leg veins vary depending upon vessel diameter (see Table 16.2).[6]

A physician employing laser therapy should routinely consider the utility of laser and intense pulsed light (IPL) technologies versus that of sclerotherapy for the treatment of lower extremity vessels.[7] The fundamental requirements for a laser or IPL source in the treatment of leg veins are delineated in Box 16.2.

Laser technology and its role in leg vein reduction is rooted in the molecule hemoglobin and its absorption spectrum, which has broad peaks at 410, 540, and 577 nm and smaller peaks at 920 and 940 nm. The spectra of oxy- and deoxyhemoglobin differ, with bluer veins responding to wavelengths targeting the deoxyspectrum; whereas red varicosities respond more effectively to wavelengths targeting the oxyhemoglobin spectrum (see Figure 16.1). Generally speaking, any vessel that is less than 3 mm in diameter may be treated by laser and IPL technologies. However, sclerotherapy is a more efficient modality for eradicating cannulable vessels, and when small, difficult to cannulate vessels are present microsclerotherapy may be implemented. Microsclerotherapy, however, is plagued by a number of adverse sequelae, increased incidence of bruising and pigment dyschromia, puncture marks from needle use, microulcerations, and inconsistent results (see Table 16.3). Given the adverse aesthetic outcomes of such procedures, the use of lasers has gained momentum in the management of cosmetic veins.

Lasers and intense pulse light (IPL) have not become replacements for sclerotherapy, primarily because hydrostatic pressure considerations are not addressed by light endothelial interactions. It is also more difficult to have

sufficient penetration of photons safely through the thick epidermal-dermal wall surrounding the lower extremity vessels when utilizing noninvasive treatment modalities like laser technology; direct injection into the target chromophore is intuitively more efficient. Furthermore, an altered pattern of cytokine release may be observed when using laser technology, resulting in injury to the vessel that may lead to increased incidence of postinflammatory hyperpigmentation.

Wavelength, pulse duration, and spot size are the parameters that are most influential during the treatment and management of individual vessels (see Table 16.4). The larger vessels tend to respond to longer wavelengths or the ratio of vessel to epidermal heating increases the probability of achieving complete vessel coagulation.[8] Shorter wavelengths, in contrast, partially coagulate the vessel ultimately increasing the incidence of treatment failures, and subsequent epidermal damage including hyperpigmentation.[9] Maximum efficiency of vessel clearance is achieved when the penetration depth of the beam equals the vessel diameter. The spot size should be as large as possible, at least on the order of 4× the optical penetration depth. An adequate spot size minimizes scattering losses in addition to maximizing beam penetration, which increases the probability that pan endothelial destruction will be achieved. The disadvantage to this, however, is that the use of larger spot sizes increases the pain and discomfort subjectively reported by the patient.

These parameters have influenced and spurred the development of a bimodal, dual-wavelength approach for the treatment of both red and blue lower extremity veins (see Figure 16.2). For the treatment of small, reddish telangiectasias with a high degree of oxyhemoglobin, short wavelengths (500–600 nm) were found to be most effective; longer wavelengths (800–1100 nm) were found to be most effective for the treatment of deeper, blue telangiectasias and reticular veins.

With continuing advances, laser technology can now address both variations in vessel size and depth with a single long wavelength 1064 nm Nd:Yag laser utilizing a varied pulse width as the monomodal approach (see Table 16.5).

TABLE 16.3 Microtelangiectasia <0.5 mm: Comparison of Microsclerotherapy and Laser Technology

	Microsclerotherapy	Laser
Number of Treatments	–	–
	–	–
		–
		–
Bruising	–	+
Discomfort	–	+
Clinical Efficiency	–	+
Purpura	–	+
Pigmentation	–	–
	–	–
		–
Ulceration	–	+
Cost	+	–
Patient Satisfaction	–	+
Physician Skill	–	–
	–	–

TABLE 16.4 Optimal Laser Parameters for the Treatment of Leg Veins

Wavelength	530–1064 nm
Pulse Duration	2–100 ms
Fluence	30–150 J/cm^2
Spot Size	1.5–10 mm

Adapted from Sadick 2002.

TABLE 16.5 Monomodal Approach to the Treatment of Leg Veins Using the 1064 nm Nd:YAG Laser

Vessel size	Spot size	Fluence	Pulse duration
<1 mm red	Small	High	Short
1–3 mm (blue)	Large	Moderate	Long

Adapted from Sadick 2003.

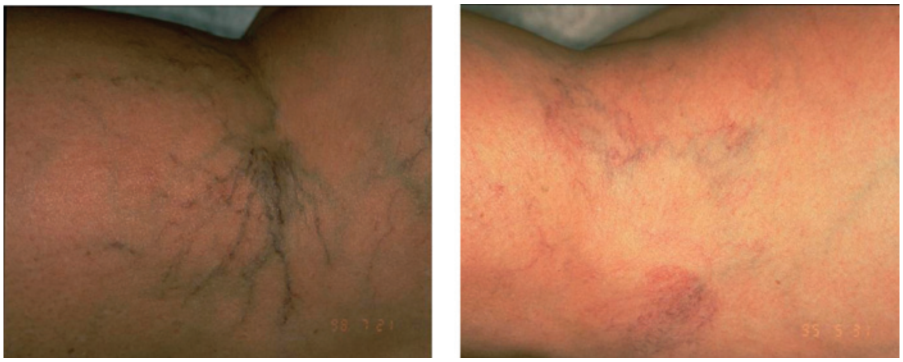

FIGURE 16.2 Pre- and post-clinical pictures of lower extremity veins using biomodal technique.

Delicate, red vessels <1 mm in diameter are superficial, having high oxyhemoglobin saturation. Consequently, they can be treated effectively with small spot sizes (<2 mm), higher fluences (350–600 J/cm^2), and short pulse durations (15–30 s). Larger blue vessels, in contrast, are typically 1–4 mm in diameter, deeper, and possess a lower oxygenated hemoglobin component. As a result, these veins are effectively treated with larger spot sizes (2–8 mm), moderate fluences (100–350 J/cm^2), and long pulse durations (30–50 ms). With the use of the Nd:YAG rapidly gaining momentum, the transition from a bimodal wavelength technique to a monomodal approach has evolved.

TREATMENT APPROACH

Candidates for Laser Therapy

Laser therapy may be considered appropriate in patients who are needle phobic, cannot tolerate sclerotherapy, are plagued by legs veins that are sclero-resistant, and/or are susceptible to telangiectatic matting (see Box 16.1). Ideal candidates for laser treatment of leg veins previously have undergone appropriate surgery or sclerotherapy for the treatment of varicosities, incompetent perforators, and reticular veins, as well as sclerotherapy to clear the majority of superficial vessels.

Patient Interviews

Diagnosis of spider or varicose veins begins with a thorough medical history detailing potential risk factors or etiologies for vascular pathology such as hormones, prolonged standing associated with occupation, obesity, pregnancy, heredity, or aging.

Physical Examination

All potential candidates for laser treatment of leg veins should undergo a thorough physical examination. During the exam, the physician should evaluate the type and size of the leg veins, and the presence/absence of reflux or incompetent valves. The treatment algorithm (see Figure 16.3) suggests that larger varicose veins with reflux should be treated first in an effort to avoid the unsuccessful treatment of smaller telangiectasias and complications such as dyspigmentation and telangiectatic matting.

In keeping with the treatment algorithm in Figure 16.3, initial treatment should include surgical removal, stripping, or ambulatory phlebectomy of varicosities and large feeder vessels. Sclerotherapy should then follow proceeding from large to small vessels. Adhering to this treatment strategy will obliterate, on average, 80 to 90% of vessels in a single session. Laser and light therapy should be utilized in the treatment of any residual vessels including those that are too small in diameter to undergo sclerotherapy with a 30–32-gauge needle.

TABLE 16.6 Lasers and Light Sources for the Treatment of Leg Veins

Laser	Wavelength
Pulsed Dye	585–605 nm
KTP	532 nm
Alexandrite	755 nm
Diode	810 nm
Nd:YAG	1064 nm
Intense Pulsed Light	515–1200 nm

LASER TREATMENT SYSTEMS

A compilation of laser and intense pulsed light sources utilized in the setting of laser treatment of legs veins are presented herein and summarized in Table 16.6. The wavelengths of light range from 515 nm to 1064 nm, depending on the treatment system employed. As mentioned earlier in the chapter, the longer the wavelength, the greater the depth of penetration, as illustrated in Figure 16.4.

578 nm Copper Bromide (CuBr) Yellow Light Laser

A new yellow light laser employing a copper bromide medium has demonstrated efficacy in the treatment or red lower extremity telangiectasia that are less than 2 mm in size. An average of 1.7 patient sessions produced significant clearing of 75% to 100% in 71.8% of patients. The positive results have been confined to the treatment of red vessels (1 mm).[10]

PULSED LASERS AND LIGHT SOURCES

Potassium-Titanyl-Phosphate Laser

For small telangiectatic leg veins in fair-skinned patients, the pulsed KTP laser has become the treatment of choice. The Versapulse KTP laser (Lumenis, Santa Clara, California, U.S.) uses the following parameters: a spot size of 3–5 mm, pulse duration of 10–15 ms, and fluences of 14–20 J/cm^2, which have proven to be effective. A 4°C chilled tip provides epidermal protection. Side effects include transient erythema, crusting superficially, and purpura. When administering the pulsed KTP laser, lower fluences must be employed in the

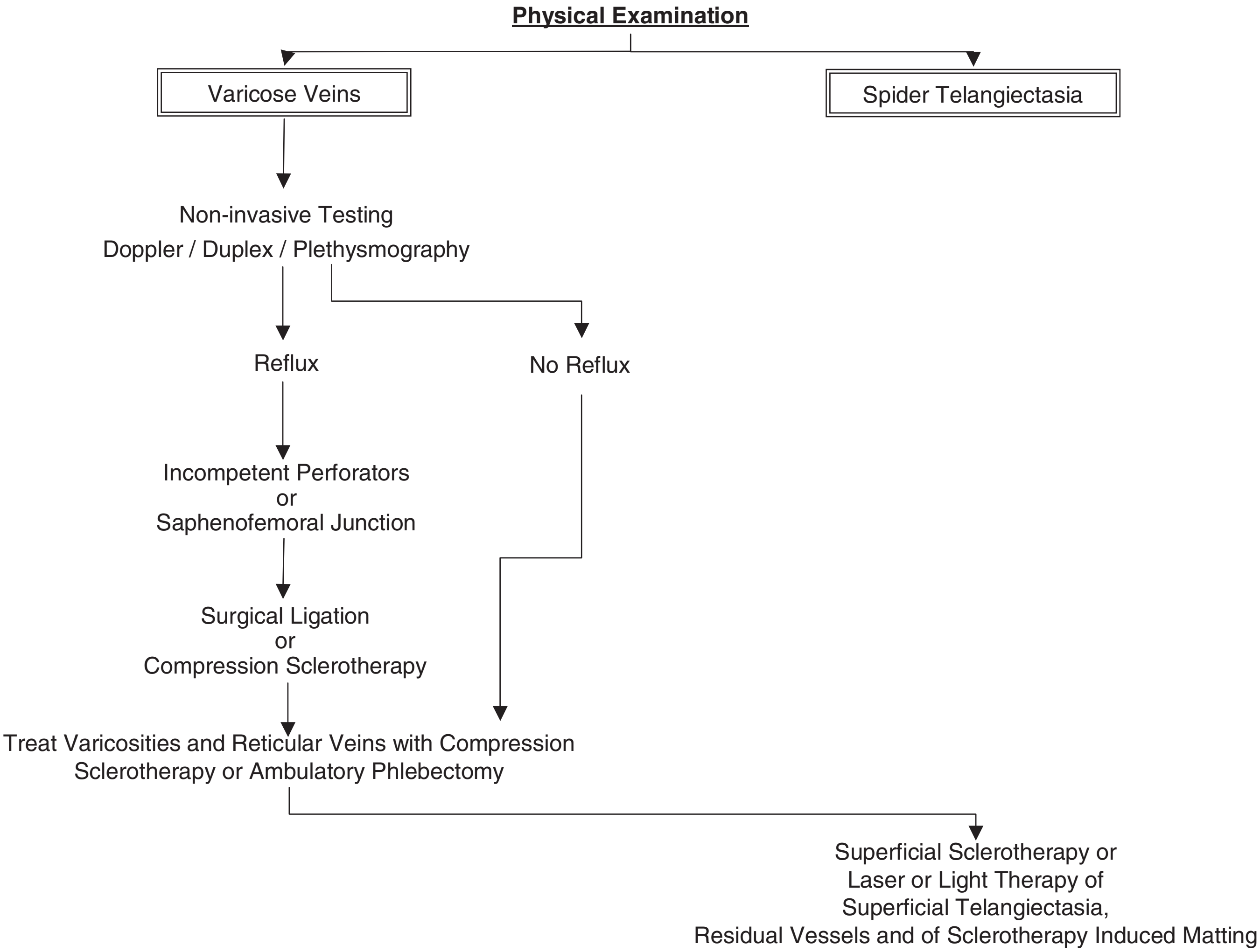

FIGURE 16.3 Systematic approach to the treatment of leg veins.

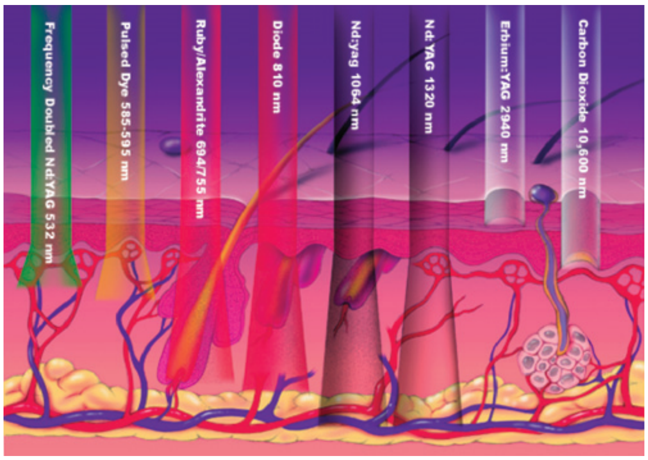

FIGURE 16.4 Wavelength and depth of penetration.

darker skinned or tanned patient because of their increased melanin and its absorption of green light. This increased absorption is more likely to increase the risk of epidermal damage. Treatment failure, consequently, is higher in this subset of patients because the lower fluences are not very effective in coagulating the target vessel. Patient acceptance of this laser treatment system is high with minimal treatment discomfort of the longer penetrating wavelengths and a relatively uncomplicated postoperative course.[11] Other technologies including the Aura (Laserscope, San Jose, California, U.S.) have produced comparable results.

Flashlamp-Pumped Pulsed Dye Laser

The pump pulsed dye laser was the first laser to achieve notable results in the treatment of leg veins in the 1980s. This treatment system utilizes short wavelength technology, at a wavelength of 577 nm. This has become acceptable for treatment of leg vessels <1.0 mm, but cannot be

recommended for treatment of blue vessels or red vessels >1.0 mm given its short wavelength, relatively short pulse duration, and moderate energy fluence.[12] This system, in contrast to long wavelength technologies, is less effective, and is associated with a number of side effects including bruising and post-therapy hyperpigmentation.

Longer Wavelength Pulsed Lasers

With the advent of longer wavelength technologies, including the long-pulsed alexandrite laser and 1064 nm Nd:YAG, longer pulse duration lasers and light sources, there has been a great increase in treatment outcomes. Presently, there are several long-pulse dye lasers available with variable pulse durations capable of deeper penetration into the skin and treatment of larger caliber spider and feeding reticular veins of the lower extremity.

Long-Pulsed Alexandrite Lasers

This system recently has been applied to the treatment of leg telangiectasia and reticular veins, less than 3 mm in diameter, with good results. The longer wavelength (755 nm) provides deeper tissue penetration and an ability to treat larger diameter and more deeply situated vessels. Although hemoglobin absorption of this wavelength is lower than that of 532 and 595 nm wavelengths, it is sufficient to achieve photocoagulation of a wide range of vessel sizes with the use of higher fluences. Optimal treatment parameters for the long pulsed alexandrite laser include 20 J/cm^2, double pulsed at a repetition of 1 Hz. To penetrate tissue more deeply and to allow greater thermal diffusion time to treat larger vessels, the alexandrite laser has been modified to provide pulse duration of up to 20 milliseconds. Side effects include purpura, matting, and long-term pigmentary alterations due to melanin absorption.

In a recent study, the alexandrite laser system evoked a significant inflammatory response with concomitant purpura and matting when used at a fluence of 60–70 J/cm^2 and a wavelength of 755 nm, in comparison to other available laser treatment systems. A study conducted by Eremia et al. concluded that the 755 nm wavelength utilized by the alexandrite system is limited to use in nontanned patients with I–III skin types.[13]

Diode Lasers

The diode lasers utilize a wavelength of 800 nm at 5 to 250 millisecond duration, and have been indicated in the treatment of superficial leg telangiectasis and reticular veins. This technology system with near infrared wavelengths allows deeper tissue penetration with decreased absorption of melanin. The efficaciousness of the diode was demonstrated in a study conducted by Garden et al. The patients, having a vessel size between 0.2 to 0.5 mm, were treated with an 810-nm quasi-continuous diode laser 20 millisecond pulse duration. The results of the study showed a 60% mean vessel clearance after a mean of 2.2 treatment sessions.[14] With the recent introduction of higher fluence capability, the diode laser's efficacy continues to increase.[4,15]

Long-Pulsed Nd:YAG Laser (1064)

The treatment of choice for spider and feeding reticular veins has become the long-pulsed Nd:YAG laser (1064). As discussed earlier in the chapter, spot sizes, energy, and pulse duration can be adjusted to target both small telangiectasias and larger reticular veins with a single device. In addition, this system via its utility of a longer, deeper penetrating wavelength and subsequent epidermal bypass increases the efficacy of this system in treatment of darker skin phenotypes. This system also addresses issues stemming from the hydrostatic pressure of feeder and reticular veins because veins up to 3 mm can be treated, although the patient's tolerance to pain may become an issue as pain increases with treatment of larger vessels. The newer pulsed 1064 nm lasers have pulsed durations between 1 and 200 milliseconds [Vasculight Lumenis (Palo Alto, California, USA), Cool touch Vantage (San Jose, California, USA), Cool Glide Excel (Burlingame, California, USA), Lyra (Laserscope, San Jose, California, USA), Gemini (Laserscope, San Jose, California, USA), and Sciton Profile, Sciton (Palo Alto, California, USA)]. For superficial vessels less than 1 mm in diameter, the optimal parameters include small spot sizes of <2 mm, short pulse durations of 15–30 ms, and high fluences of 350–600 J/cm^2. For reticular veins, 1 to 4 mm in diameter, larger spot sizes (2–8 mm), longer pulse durations (30–60 ms), and moderate fluences (100–370 J/cm^2) should yield successful results. As a result, the Nd:YAG laser has been embraced by many clinicians worldwide as the state of the art for laser treatment of lower extremity vessels.

The Lyra and Gemini systems use contact cooling and encompass a 1064 nm Nd:YAG technology. Seventy-five percent improvement of veins of all colors and sizes has been reported with this technology. The Sciton Image has been used predominantly for treatment of the lower extremity telangiectasias and reticular veins up to 3 mm in diameter. Its high energy fluence and large spot size have increased its efficacy in treating both large diameter vessels (i.e., reticular veins and small capillary mats less than 1 mm in diameter). A static cooling device also is employed in this treatment system. The Vasculight also has been utilized for

treatment of both smaller vessels and larger reticular veins up to 4 mm in diameter. The operator applies a coupling cooling gel in addition to an internal DCD (1–4°C) and applies the laser tip directly to the treatment vessel under consideration. Superficial red telangiectasias less than 1 mm in diameter may be treated with the hand piece coagulated and defocused off the skin and a lower energy fluence of 90–100 J/cm^2 with a pulse duration of 10 to 12 milliseconds delivered as a single pulse.

Weiss et al. achieved 75% improvement at the three-month follow-up of 0.3 to 3.0 mm vessels documented by Duplex closure. Settings in this study including fluence of 80 to 120 J/cm and single-pulse durations of 10 to 30 milliseconds were utilized.[16] Sadick et al. treated 20 patients with Fitzpatrick skin type II to IV with a similar technology. A mean of 2.5 treatments produced 100% clearance in 88% of patients. Mild purpura was noted in 20% of patients, and post laser hyperpigmentation was noted in 10% of patients.[17]

INTENSE PULSED LIGHT

Intense pulsed light (IPL) devices have also been indicated in the treatment of leg veins, albeit with variable results. These systems have been shown to have dual success in penetration of both superficial and deep tissues, in addition to absorption by both oxygenated and deoxygenated hemoglobin (Photoderm VL, Vasculight IPL, Lumenis, Palo Alto CA, U.S.). The main advantage of IPL technology in the treatment of leg veins has been the use of large spot sizes, causing minimal purpura. This technology, in contrast to other treatment modalities, uses a noncoherent pulsed light source with wavelengths between 500–1200 nm, emitting a spectrum of light rather than a single wavelength in single, double, or triple pulses. The results of this current system are variable. Schroter et al. reported immediate clearing in 73.6% of patients and in 84.3% of patients after four weeks. With respect to the immediate response, 82% clearing was seen in the group with veins up to 0–2 mm, 78.9% was seen in the group from 0.2 up to 0.5 mm, and 59.7% was seen in the groups from 0.5 to 1.0 mm.[18]

Other investigators, in contrast, have found lesser success utilizing this technology for management of lower extremity spider veins. Results from a study done by Green showed no improvement in 56% of patients, partial clearing in 25% of patients, and no improvement in 56% of telangiectasias. It is worth mentioning that this particular study was done at the incipient stages of the IPL system's development.[19] Associated side effects include blistering, crusting, and discoloration, especially in darker skinned patients. With growing sophistication and use, however, IPL stands at the very forefront of laser vein technology, being the most effective for treating telangiectatic matting associated with diffuse erythema.

COMBINED LASER/RADIOFREQUENCY TECHNOLOGIES

The most recent development in laser technology in the treatment of leg veins is the combination of bipolar radiofrequency and optical energy, using either the diode laser or an intense pulsed light source. The basis of this technology is rooted in the idea that the two forms of energy act synergistically to enhance clearance of the target vessel; with utilization of this system a high energy penetration depth (>2 mm) and a high energy density on the treated vein (>100 J/cm^2) can be achieved. The laser component selectively heats the vessel, allowing the preferential absorption of radiofrequency energy because of the increased temperature and the high electrical conductivity of blood. Moreover, this system has demonstrated 80% clearing of vessels <3 mm in diameter after an average of 2.5 treatment sessions by the author.

ADMINISTERING LASER THERAPY

Most laser therapy patients tolerate treatment without difficulty. If a patient exhibits increasing sensitivity to pain or if larger telangiectatic or reticular veins are being treated, a topical anesthetic cream should be applied one hour prior to treatment and covered with a plastic dressing. Once the area has been numbed adequately, the area should be cleansed with alcohol. The physician, patient, and any medical assistants present during treatment should wear protective eyewear.

When using the 532 nm KTP laser in the treatment of smaller telangiectasias, a spot size of 3–5 mm, fluence of 12–20 J/cm^2, and a pulse duration of 10–15 is recommended. Skin cooling, as discussed earlier in the chapter, should be used before, during, and after treatment to prevent thermal damage to surrounding tissues and decrease patient discomfort. Laser pulses should then be applied individually, separated by at least 1–2 mm. Each laser pulse should be traced along the length of the vein with no overlap or double pulse. A minimal amount of pressure with the application device should be applied to avoid compression of the selected target vessel. The goal of treatment should be either vessel spasm with immediate clearance or thrombosis with darkening of the vessel. Typically patients require two to three treatment sessions with 6- to 12-week nontreatment intervals because of the intense cytokine release generated by the laser endothelial interaction for maximal results. However, complete clearance may be achieved following one treatment.

For reticular or telangiectasias >1 mm long pulsed Nd:YAG laser is the treatment of choice. The 1064 nm lasers possess the ability to vary spot sizes, pulse width parameters, resulting in a wide treatment range of leg veins includ-

ing small telangiectasias. For superficial vessels less than 1 mm in diameter, the optimal parameters include small spot sizes of <2 mm, short pulse durations of 15–30 ms, and high fluences of 350–600 J/cm^2. For reticular veins 1 to 4 mm in diameter, larger spot sizes (2–8 mm), longer pulse durations (30–60 ms), and moderate fluences (100–370 J/cm^2) yield successful results. As with other laser modalities, cooling before, during, and after the pulse protects the patient's epidermal layer from damage when using higher fluences, and also increases patient comfort. With application of this system, it is often useful to apply mild pressure with the hand piece when treating reticular veins to minimize the diameter and the amount of hemoglobin in the lumen. This allows greater vessel penetration with less total heat and reduced thermal damage to surrounding skin/tissue. After treatment with the Nd:YAG laser, small vessels experience immediate resolution; larger telangiectasias and reticular veins experience no visual change during the treatment, but demonstrate improvement and ultimately clearance within weeks to months following treatment.

Complications following treatment with any laser system include swelling, urtication, or erythema around the treated vessels. The aforementioned side effects may resolve quickly with the application of ice packs, or a topical steroid. Application of this treatment may also decrease the risk of post-inflammatory hyperpigmentation. Although compression stockings are considered unnecessary after the treatment of small telangiectasias, they may improve results if worn one week following the treatment of larger telangiectasias and reticular veins by preventing vessel refilling.

THE BENEFITS OF LASER THERAPY

With its increasing momentum, laser therapy has become one of the most effective treatment options for treating varicosities of the lower extremity. Generally at the time of treatment, both the patient and the physician may observe a disappearance of small telangiectatic vessels giving an immediate visual record of success of treatment. However, the larger telangiectasias and the deeper reticular veins typically do not demonstrate resolution at the time of treatment, often resolving gradually over the course of several months.

A recent study using the monomodal approach with the 1064 nm Nd:YAG and variable spot sizes and pulse width parameters to treat spider telangiectasias and reticular veins produced the following results: Twenty percent of the treated vessels exhibited a 50 to 75% improvement after three treatments administered following one-month intervals. Gradual improvement was observed at the six-month follow up visit, with 80% of the treated vessels exhibiting 75% clearing. Ninety percent of patients were highly satisfied with the treatment.[20]

Another comparative study examined the effectiveness of the 1064 nm Nd:YAG versus the 810 nm diode and the 755 nm alexandrite lasers in the treatment of 0.3–3 mm in diameter. The results summarized in Table 16.1 demonstrated that the Nd:YAG laser was the most effective treatment modality at three months follow up. Purpura and matting were problematic with the alexandrite laser; the results produced by the long-pulsed diode were unpredictable in the subjects enrolled.[13] Presently, no long-term controlled studies have been done regarding the persistence of vessel clearing after laser treatment of leg veins.

ROLE OF COOLING AND OTHER ADVANCES IN LASER TECHNOLOGY

The development of cooling devices (Chess Chamber, VersaPulse, Chill Tip, IPL Chiller, Zimmer Cooler) provides epidermal bypass, which protects the epidermis from damage, allowing delivery of higher fluences of energy. As a result, contact or dynamic cooling devices are presently incorporated into all devices currently manufactured. The increased utilization of extended pulse durations also allows delivery of greater amounts of energy in a more gentle fashion providing more consistent pan-endothelial destruction, translating into more consistent results with fewer treatments and lesser side effect. To date the pulse duration most suited for the thermal destruction of leg telangiectasias appears to be 1–50 msec. Other advances including those made in gentle cavitation, captured pulsing, and the regular use of large diameter beams have all lead to improvements in laser/IPL technology.[21]

ADDRESSING THE COMMON PITFALLS IN LASER THERAPY

The laser treatment of leg veins is not free of common pitfalls (see Box 16.3). Retreatment or double pulsing of the target vessels vessel should be avoided to prevent excessive thermal damage that potentially can result in scarring and ulceration. The physician or the medical personnel admin-

BOX 16.3 Common Pitfalls

- Avoid immediately retreating or double-pulsing vessels when no instantaneous changes are present.
- Allow treated areas to cool before attempting a second pass.
- Always use the lowest possible effective fluence.
- Space adjacent laser pulses at least 1–2 mm apart to reduce excessive thermal damage.

BOX 16.4 Side Effects

- Transient hyperpigmentation
- Purpura
- Telangiectatic matting
- Pain
- Thrombosis
- Epidermal damage
- Incomplete clearance

istering the treatment should be aware that change of the target vessel may take up to several minutes given the time that it takes for thermocoagulation to occur even when the appropriate parameters are utilized. In the setting of a clearly resistant vessel, it is better to work on a distinctly separate treatment area and return to the resistant vessel in 5 to 10 minutes. It is also important to use the lowest possible fluence that will effectively treat a selected vessel to minimize complications. As a rule a rule of thumb, the physician should always start at the lowest fluence and incrementally increase to higher energy levels as needed depending on the vessel response. Blanching of the skin is a physical manifestation of excessive thermal injury and should be avoided at all costs. Furthermore, the physician should take note of the lateral spread of the thermal energy into surrounding areas, particularly with the longer wavelength 1064 nm laser. Nontreated vessels connected to or adjacent to the desired treatment pulse area may receive enough thermal damage to unintentionally coagulate. All pulses, consequently, ideally should be separated by 1–2 mm. Because of high cytokine, treatment sessions should be spaced at least six to eight weeks apart in order to reduce the risk of post-inflammatory hyperpigmentation.

Side Effects, Complications, and Alternative Approaches

Complications of the laser therapy of leg veins include epidermal damage, thrombosis, hyperpigmentation, matting, and incomplete clearance (see Box 16.4). During the actual procedure patients typically complain of discomfort, but rarely do they feel uncomfortable postoperatively. For those patients who develop telangiectatic matting of incomplete vessel clearance, retreatment should be offered with either laser or microsclerotherapy as deemed appropriate. Localized areas of thrombosis may resolve independently from treatment or easily can be expressed with an 18-gauge needle. Post-procedure hyperpigmentation is usually transient and has become less of an issue with the advent of the longer wavelength technologies and improvement of epidermal cooling devices. Moreover, wound care should follow any procedure that results in epidermal damage, thereby decreasing the incidence of scarring.

THE FUTURE OF LASER THERAPY

The laser treatment of leg veins continues to gain momentum with advances in laser, pulsed light, and combined radiofrequency pulse light technologies. Other advances include enhancement of longer wavelength treatment systems, improved cooling technologies, varied spot size, pulse durations, and fluence-related monomodal approaches and combined lasers/radiofrequency systems. The continued development of laser technologies not only enhances the phlebologist's armamentarium in the treatment and management of telangiectasias and reticular veins, but also provides the patient with an array of safe, noninvasive treatment options with minimal side effects or complications.

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CHAPTER

17

Overview: Treatment of Venous Insufficiency

JOHN BERGAN

The term venous insufficiency implies that normal functioning is deranged. Terms used to describe the various manifestations of venous insufficiency lend confusion to the general topic. Some of these terms, such as telangiectasias, thread veins, and spider veins are descriptive but imply different conditions. And it is in the chronic disorders, dominated by venous reflux through failed check valves causing hyperpigmentation, ulceration, and corona phlebectatica, where disorientation reigns. Some order can come from subscribing to a unifying theory of primary venous insufficiency and of a common theory of effects of an inflammatory cascade that clarify both situations.

PRIMARY VENOUS INSUFFICIENCY

The manifestations of simple primary venous insufficiency appear to be different from one another. However, reticular varicosities, telangiectasias, and major varicose veins are all elongated, dilated, and are tortuous. Investigations into valve damage and venous wall abnormalities eventually may lead to an understanding of the problem, and therefore, a solution by surgery or pharmacotherapy.[1–4]

Scanning electron microscopy has shown varying degrees of thinning of the varicose venous wall. These areas of thinning coincide with areas of varicose dilation and replacement of smooth muscle by collagen, which is also a characteristic of varicose veins.[5,6] Our approach to this has been to assume that both the venous valve and the venous wall are affected by the elements that cause varicose veins. We and others have observed that in limbs with varicose veins, an absence of the subterminal valve at the saphenofemoral junction is common.[7] Further, perforation, splitting, and atrophy of saphenous venous valves have been seen both by angioscopy[8,9] and by direct examination of surgical specimens.[10]

Supporting the theory of weakness of the venous wall leading to valvular insufficiency is the observation that there is an increase in the vein wall space between the valve leaflets.[10] This is the first and most commonly observed abnormality associated with valve reflux.[11] Realizing these facts, our investigations have led us to explore the possible role of leukocyte infiltration of venous valves and the venous wall as part of the cause of varicose veins. In our investigations of surgical specimens, leukocytes in great number have been observed in the venous valves, and wall and monoclonal antibody staining has revealed their precise identification as monocytes.[10] Similar findings are present in the skin of patients with venous insufficiency.[12]

SURGICAL TREATMENT

Removal of the Great Saphenous vein (GSV) from the circulation is one of two essential steps in treating lower limb varicose veins. Incompetent valves along the GSV allow blood to reflux down the vein and into its tributaries, transmitting high pressure into smaller tributaries, which become varicose as a result. Much emphasis has been placed on the correct technique of high sapheno-femoral ligation, in which meticulous attention is paid to identifying, ligating, and dividing all the tributaries of the GSV as they join the vein in the groin. It has always been a matter of surgical dogma that overlooking any of these allows continued reflux into the residual tributary and subsequent development of recurrent varicose veins.

A number of studies have confirmed that patients in whom the GSV is stripped tend to have fewer recurrences

than those undergoing simple high ligation of the Saphenofemoral junction (SFJ). Sarin et al. studied 89 limbs in 69 patients with LSV incompetence.[13] Legs were randomized to SFJ ligation with or without stripping, and evaluated by photoplethysmography (PPG), duplex scanning, clinical examination, and patient satisfaction. The follow-up period was 18 months. Significant differences in favor of the stripped group were found in all four parameters at final evaluation

A similar study of 78 patients (110 limbs) was reported by Dwerryhouse et al. in 1999, with a longer follow-up period of five years.[14] This demonstrated a significantly lower reoperation rate among patients undergoing GSV stripping (6%), as opposed to 20% in those undergoing high SFJ ligation alone.

Duplex scanning showed a much lower incidence of residual reflux in the remaining GSV when the proximal vein had been stripped to the knee than when it had not. However, the patient satisfaction rate was not significantly different between the two groups. Ninety percent of the stripped groups were satisfied as opposed to 87% in the nonstripped group (p = ns).

A further study from Jones et al. came to similar conclusions.[15] One hundred patients (133 limbs) were randomized as before. After two years, 43% of those who had not had GSV stripping demonstrated recurrent varicose veins as opposed to 25% who had. There was a statistically significant difference.

NEOVASCULARIZATION

Of great importance was the fact that duplex scanning showed that neovascularization in the groin was the commonest cause of varicose recurrence. It was often seen in the ligation group that reflux through the neovascularization entered the residual saphenous vein and perpetuated the old varices while new ones developed. The authors concluded that by stripping the GSV, one was removing the run-off into which the new vessels could drain. Again, however, the satisfaction was broadly similar between the two groups: 91% in the stripped group and 87% in the unstripped.

All these authors concluded that stripping the long GSV gave better long-term results than simple high saphenous ligation. This appears to be true in terms of objective assessment of recurrence rates and in objective measurement of post-operative venous function but is not generally reflected in patient satisfaction rates, which tend to be similar whichever procedure is performed. This led Woodyer and Dormandy to reach a contrary conclusion—that stripping the LSV was a procedure based on surgical dogma, and one that did not confer subjective benefit to the patients so treated.[16] This leads one to conclude that a better method of evaluation of treatment results should be developed.

NONSURGICAL TREATMENT

In recent years, endovenous ablation has been found to be safe and effective in eliminating the proximal portion of the GSV from the venous circulation, with even faster recovery and better cosmetic results than stripping.[17,18] The two currently available methods used to achieve ablation of the GSV are the Closure© procedure using a radiofrequency (RF) catheter and generator (VNUS Medical Technologies, Inc., Sunnyvale, California), and the endovenous laser ablation (EVLT) procedure using a laser fiber and generator (various manufacturers). Both systems use electromagnetic energy to destroy the GSV *in situ*.

One of the difficulties in evaluating reports of successful ablation of the Great Saphenous vein lies in the definition of success. Some, especially in the RF ablation reports, define success as "no reflux in any segment longer than 5 cm." Some laser reports refer to success as "stable occlusion" or "reduction in reflux," and Min has applied the much clearer standard of success as "no flow by color flow Doppler."[17] Those who report results have not used the life table method, which takes into consideration drop outs and early and mid-term failures. Thus the reported favorable four and five year rates of elimination of reflux may be exaggerated.

The major difficulty with defining success as reduction or absence of reflux is that attempts to establish whether reflux is present in a portion of a previously closed GSV may be inaccurate. Also, most recurrent patency is seen in the proximal portion of the treated GSV. Therefore, distal compression of the closed portion of the GSV to identify reflux in a proximal segment is futile. Likewise, using the Valsalva maneuver is unreliable and lacks reproducibility. Finally, the importance of distinguishing a partially patent channel with flow, from one with reflux, is academic, since the valves are just as thoroughly destroyed as the rest of the vein wall.[19]

Initially, reports of successful ablation of the GSV using either radiofrequency or laser energy without ligation or stripping were treated with great skepticism. However, the absence of neovascularization is striking and many skeptics have begun to believe that former emphasis on a clean groin dissection may have been in error. Although it is still early days, acceptance of endovenous techniques is increasing. Patient acceptance of these minimally invasive procedures is overwhelmingly better than with stripping.

Choosing which procedure to adopt according to Morrison[19] is influenced by a variety of factors including reported results (and especially reporting methods); economic factors, such as equipment and disposables costs, reimbursement, procedure time; availability of and experience with ultrasound equipment and trained personnel; individual support by industry before, during, and after acquisition of the generator; and the practitioner's own level of expertise and

comfort with ultrasound-guided techniques and minimally invasive surgery.[19]

CHEMICAL VENOUS CLOSURE

Some phlebologists have advocated liquid sclerotherapy of the saphenous vein, but the results of such treatment have been disappointing, and published long-term results are absent. Comparisons between liquid and foam sclerotherapy have been done and the results strongly favor foam.[20,21] Ultrasound-guided sclerotherapy (USGS) with foam must be considered as a completely new treatment of varicose veins. Although it needs proper training and some skill, it is simple, affordable, and extremely efficient.

Sclerosing agents produce a lesion of the venous wall, predominantly of the endothelium and, to a minor extent, of the media. The reaction that follows depends on the concentration of the agent and on the duration of the contact. If the venous diameter is greater than 3 mm, injections of liquid do not achieve this aim and dilution with blood quickly decreases their efficacy at short distances from the point of injection. Injections of foam have the advantage of a total filling of the vein, at least under 12 mm diameter. A further reduction in venous diameter can be obtained by leg elevation, compression with the hand, duplex probe or bandage, and venous spasm. In very large veins, foam will float over blood and induce a lesion of the upper venous wall, despite apparent correct filling of the vein observed on duplex, thus the importance of massaging and compression.

Making the foam is easy and quick. Based on the technique initially described by Tessari, it can be prepared with two 5 cc syringes and a three-way stopcock.[20] Only detergent sclerosing agents can be used: Sotradecol and Polidocanol at any desired concentration from 0.25% to 3%. Microbubbles of foam sclerosing agents are hyperechogenic and represent an excellent contrast medium for ultrasound techniques. They appear as a shadow within the lumen early, and like a hyperechogenic mass later with a acoustic shadow. Massaging the sclerosing agent to the desired part of the varicose network with the duplex probe or the hand is also very easily carried out. Progression from the varicose clusters to the GSV and then to the SFJ is always visible, provided a sufficient volume has been injected. Venous spasm usually is observed within minutes. The importance of the initial spasm has been emphasized in several studies and protocols.[22,23]

Post-sclerotherapy compression is mandatory: on the varicose clusters for 48 hours, and then whole limb compression with 20–30 mmHg thigh-high medical elastic stockings.[24] They must be worn during the daytime for at least 15 days. Patients must be examined both clinically and with duplex at 7 to 15 days.

The absolute risk of deep venous thrombosis is not confirmed. A few cases have been reported: most of them are gastrocnemius vein thrombosis, typically after telangiectasia and reticular vein sclerotherapy. Most frequent complications are visual disorders. These adverse reactions have been observed also with liquid sclerosing agents but their incidence is much higher with foam; they can be estimated at 0.5–1 per 100 foam sessions.[25] They are observed more frequently in patients suffering from migraine with visual aura. They usually reproduce this aura. The patho-physiology of this phenomenon has been questioned but has received no answer so far. The existence of a patent foramen ovale is the most likely explanation, as has been the liberation of toxic component associated with endothelial cell destruction (endothelin).

All published results demonstrate an immediate efficacy better than 80% in terms of immediate/primary venous occlusion. Repetition of injections in case of initial failure allows closure to approach 95% of efficacy with two to three sessions. Early and mid-term results demonstrate a recurrence rate of about 20%. The re-do injections remain as simple as primary injections and at least as efficient.

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CHAPTER

18

Ultrasound Examination of the Patient with Primary Venous Insufficiency

LUIGI PASCARELLA and LISA MEKENAS

INTRODUCTION

Chronic venous insufficiency (CVI) is a common disorder whose manifestations include varicose veins, and skin changes such as venous dermatitis, hyperpigmentation, lipodermatosclerosis, and chronic leg ulcers. The constellation of signs and symptoms identifying CVI has been clearly demonstrated to be related to venous hypertension.[1,2] Several factors, such as age, gender, hormones, body posture, and genetic inheritance, are associated to the development of venous hypertension.[3] This, in turn, has been found to trigger vascular remodeling, through a reorganization of extracellular matrix within the venous parenchyma. This leads to the failure of vein valves.[4,5]

Primary valve incompetence is the most important cause of venous hypertension (70–80% of cases). Valve incompetence may be secondary to deep venous thrombosis or trauma in 18–25% and due to a congenital anomaly in 1–3% of cases.[6]

In the past, assessment of the function of the superficial and deep veins was often indirect and invasive.[7,8] Surgical textbooks devoted a great deal of space to clinical examination of the patient with varicose veins. Many of the clinical tests were described 100 years ago and carry the names of famous individuals interested in venous pathophysiology such as Schwartz, Perthes, and Trendelenburg.[9]

Evaluation of clinical findings with duplex ultrasonographic validation has shown “the clinical tests used in the examination of patients with primary varicose veins are inaccurate.”[10] A comparison of preoperative evaluations using physical signs alone, physical findings combined with hand-held Doppler examination, and physical findings combined with duplex validation revealed that a traditional clinical examination can be improved by the use of hand-held Doppler ultrasonography. However, prior preoperative planning can best be performed by incorporation of duplex technology in the examination.[11]

Direct venous pressure measurements and photoplethysmography are able to provide indirect information about the venous physiology of the lower extremity as a single but undividable system. These miss significant data concerning specific vein segments.[9] Venous anatomy is revealed by ascending and descending phlebography, and these provided more sensitive information about obstructive and post-thrombotic states. Varicography has also been used. In one study, color-coded duplex sonography was compared with phlebography supplemented with varicography. It was concluded that ascending venography was slightly superior to color-coded duplex sonography in detection of post-phlebitic changes, but there was good agreement between color-coded duplex sonography and descending phlebography in the grading of superficial and deep vein reflux. Similarly, there was agreement in evaluating Great and Small Saphenous reflux when venography and duplex scanning were compared.[12]

Increased costs, low patient acceptance, low sensitivity, and specificity in discriminating among the elements in the differential diagnosis often relegated the diagnosis of CVI to a purely clinical examination of the patient.[13]

The advent of the duplex ultrasound has provided the physician with practical information to asses varicose veins, deep veins, thrombotic states, post-thrombotic obstruction, and incompetent perforators.[8] The standardization of this testing is incomplete, but it has already uncovered new concepts of anatomy, physiology, and pathophysiology of the venous system of lower extremities.

EQUIPMENT

The ultrasound duplex scanner should be able to detect blood flow rates as low as 6 cm/sec.[13] This can be done by dedicated high resolution vascular scanners with Color/Power-Doppler functions and pulsed-wave Doppler. Linear transducers in the range of 4–7 megahertz are used.[6] The IVC, pelvic veins, and deep veins in obese patients may be be imaged with 3 megahertz transducers.

With the advances in technology, duplex scanners have become smaller, more transportable, and more operator friendly.[14] Miniaturized devices feature transducers designed with advanced architecture that allow a single probe to image across a greater range of depths within an application and across applications. The transducer for peripheral vascular examinations operates from 10–5 MHz and provides resolution from skin surface to 7 cm in depth. The technology incorporates power Doppler sonography, tissue harmonic imaging, and direct connectivity to a personal computer. Their overall performance is comparable to the more traditional ultrasound machines.[14]

Additional material needed for a complete examination include acoustic gel, towels, a walker, and a data collection diagram.

EXAMINATION

The examination should begin with a complete medical history. Data concerning family and personal venous history, symptoms, clinical findings, and previous venous treatments are collected.[13] Comorbidities, allergies, and pharmacologic history must be documented. The BMI is calculated from the patient's height and weight.

The patient should be examined in a standing up position to better demonstrate patterns of telangiectasias and reticular and varicose veins.[15,16] Cold light transillumination of the skin (vein light) may be used to identify reticular veins, and portable Doppler devices can verify the presence of reflux in some superficial veins.[16] Clinical data should be integrated into the CEAP classification.[17]

Limbs should be classified into one of seven CEAP classes of increasing severity designated C_0 to C_6 (see Table 18.1) and identified as symptomatic (S) or asymptomatic (A).[17] Common symptoms associated with CVI are leg aching, heaviness, and sensation of itching and swelling; important signs to consider are skin hyperpigmentation, blue blebs, corona phlebectatica, venous dermatitis, lipodermatosclerosis, active ulcers, and/or scars from previous ulceration. Recently the term chronic venous disease (CVD) has been referred to the full spectrum of signs and symptoms associated with classes $C_{0,S}$ to C_6, and the term chronic venous insufficiency related to classes C_4 to C_6.[18]

A history of previous deep vein thrombosis or pulmonary embolism will provide information regarding etiology. The method of making the diagnosis of DVT always should be recorded.

The anatomic distribution and the pathophysiology within the CEAP system are revealed by the ultrasound examination.

TABLE 18.1 CEAP Classification of Chronic Venous Disease and Chronic Venous Insufficiency[17]

Class	Signs of venous disease
Class 0	No visible or palpable signs of Venous Disease (only symptoms)
Class 1 (a,s)	Teleangiectasias or Reticular Veins
Class 2 (a,s)	Varicose Veins
Class 3 (a,s)	Edema
Class 4 (a,s)	Skin changes ascribed to venous disease (e.g., pigmentation, venous eczema, lipodermatosclerosis)
Class 5 (a,s)	Skin Changes as defined above with healed ulceration
Class 6 (a,s)	Skin Changes as defined above with acticve ulceration

TABLE 18.2 Summary of Important Changes in Nomenclature of Lower Extremity Veins[19,25]

Old terminology	New terminology
Femoral Vein	Common Femoral Vein
Superficial Femoral Vein	Femoral Vein
Deep Vein of the thigh	Profunda Femoris Vein
Greater/Long Saphenous Vein	Great Saphenous Vein
Smaller/Short Saphenous Vein	Small Saphenous Vein
Sural Veins	Soleal Veins
	Gastrocnemius Veins
	Medial Gastrocnemius Vein
	Lateral Gastrocnemius Vein
	Intergemellar Vein
Dodd's Perforator	Perforator of the Femoral Canal
Boyd's Perforator	Paratibial Perforator (upper third of the leg)
Sherman's Perforator (24 cm)	Paratibial Perforator (mid third of the leg)
Cockett's Perforators	Posterotibial Perforators

ULTRASOUND EXAMINATION

In 2002, an International Interdisciplinary Consensus on Venous Anatomical Terminology proposed a revision and extension of the Terminologia Anatomica of the lower extremity venous system (see Table 18.2).[19] The new nomenclature has been fully adopted in this chapter.

The ultrasound examination is carried out with the patient standing in an upright position.[20] This position elicits reflux by challenging venous valves and maximally dilates the leg veins. Sensitivity and specificity in detecting reflux are increased in examinations performed with the patient standing rather than when the patient is supine.[7,8,20] The supine examination should be considered to be inadequate.

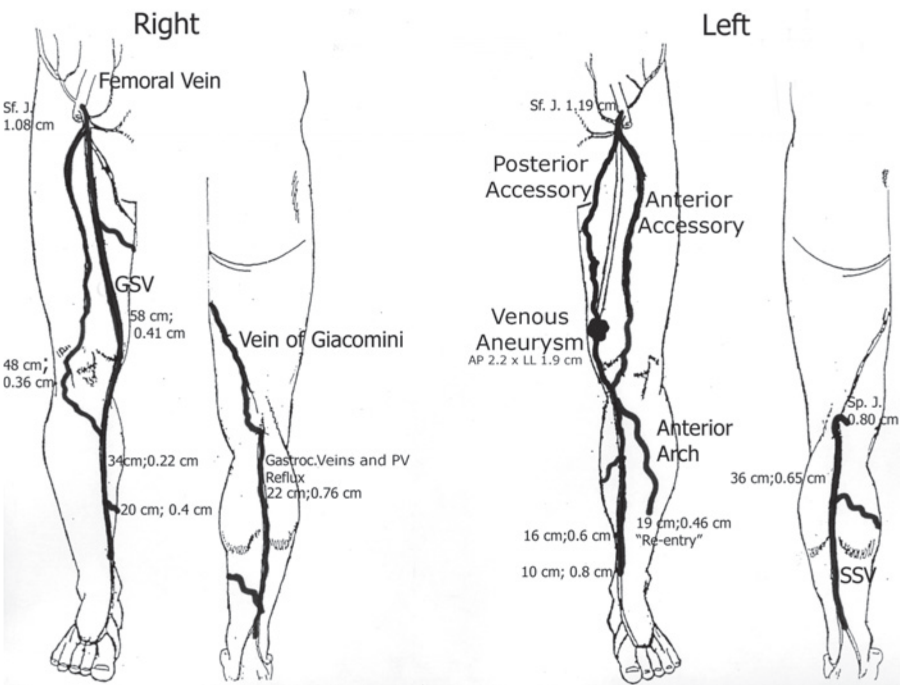


FIGURE 18.1 This data entry form outlines the saphenous veins and the relevant deep veins. Refluxing veins are added in heavy black lines. Location of perforating veins and aneurysms can be added and distance from the floor indicated. Diameters of perforating veins at the fascial level should also be noted.

Of particular importance is instruction to the patient to inform the ultrasonographer of any lightheadness, faint feeling, dizziness, or nausea. These symptoms seem to be associated with the overall atmosphere of the room and the audibility of Doppler velocity signals. The symptoms appear less frequently in patients when the examination is performed silently. If such a tendency to fainting because of vaso–vagal reflux is encountered, the examination may need to be modified with the patient in the semi-upright position.[14]

The veins are scanned by moving the probe vertically up and down along their course. Duplicated segments, sites of tributary confluence, and large perforating veins and their deep venous connections are identified.[14]

Transverse rather than longitudinal scans, and continuous scanning are performed in order to provide a clear mapping of the venous system.[14] This can be recorded on a premade datasheet (see Figure 18.1). Patency usually is assessed by compression of the vein, and reflux is detected on release. The augmentation of flow, distal compression, and release of thigh and calf[6] should be done sharply and quickly.[14] Automated rapid inflation/deflation cuffs are cumbersome but may be used for this purpose, and offer the advantage of a standardized stimulus.[8,15] The Valsalva maneuver is a reverse flow augmentation stimulus and is used only for the Sapheno-femoral junction (SFJ) because a competent valve will render the test useless distally.

REFLUX

The presence of vein reflux through incompetent vein valves is the most important pathologic finding in CVI. Reflux is measured during the release phase of the flow augmentation maneuver and during the closed-epiglottis apneic phase of the Valsalva (see Figure 18.2). It should be noted that retrograde backflow is present in normal vein valves immediately before their closure, but a cutoff value of 500 ms defines pathologic reflux in superficial, profunda femoris, and deep calf veins. The value of 350 ms is used in perforator veins and 1000 ms for femoral, superficial, and popliteal veins.[20,21]

THE SAPHENO-FEMORAL JUNCTION

With the patient standing and the transducer gently applied in the groin, the SFJ, common femoral vein, superficial femoral vein, and profunda femoris veins are identified (see Figure 18.3). The SFJ is complex and highly variable. It includes the Great Saphenous vein (GSV), pudendal veins, and superficial epigastric and superficial circumflex iliac veins (see Figure 18.4a).[19,22] Imaging of the pudendal veins is particularly important in cases of Pelvic Congestive Syndrome in which vulvar varicosities and pudendal reflux can

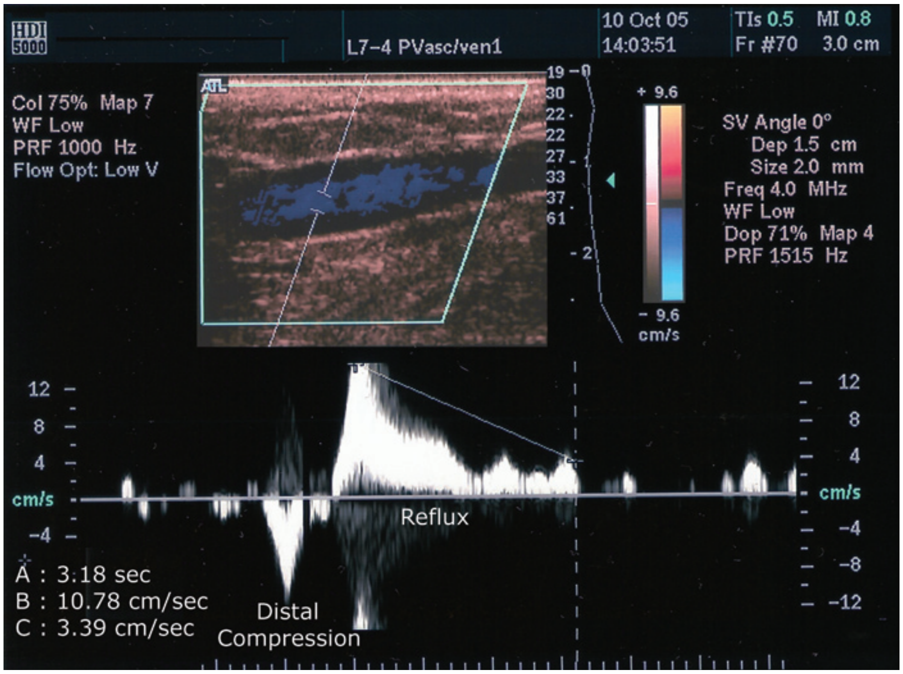


FIGURE 18.2 Flow augmentation maneuvers elicit reflux in incompetent veins. Reflux is defined as retrograde outflow measured during the release phase of the augmentation maneuver and the Valsava's closed epiglottis apneic phase for the saphenofemoral junction only. Cuttoff values for different veins are listed in the text.

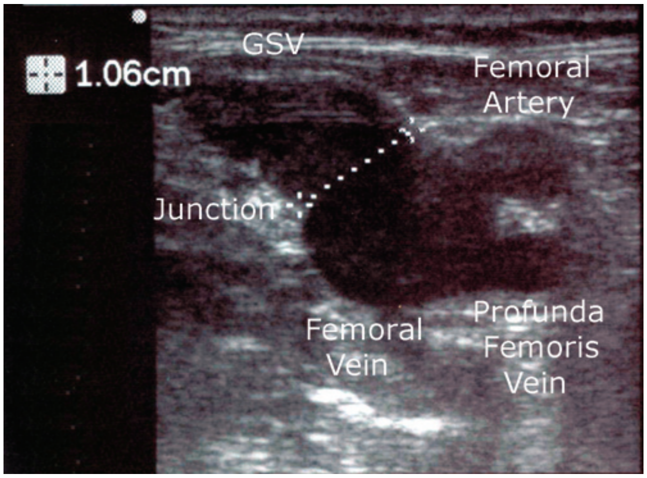


FIGURE 18.3 A transverse scan of the saphenofemoral junction is displayed. Major anatomic landmarks to be noted are femoral vein, femoral artery, profunda femoris vein, junction (diameter), Great Saphenous veins.

be observed.[23] Incompetence of the ovarian veins is the most important cause of this syndrome.[24]

The diameter of the SFJ at the confluence of the GSV and the femoral vein is recorded as this is important in performing endovenous therapy. The SFJ is usually the location of the terminal valve.[25] More distally another valve, known as subterminal, is also identifiable (see Figure 18.4b).[25]

The Valsalva and thigh/calf compression-release maneuvers define the presence of reflux at the saphenofemoral junction as well as in the femoral vein.

THE GREAT SAPHENOUS VEIN

The Great Saphenous vein is scanned from the groin in proximal-to-distal direction.

In the thigh, the GSV lies within the saphenous compartment (see Figure 18.5).[19] The superficial fascia and the muscular fascia define the saphenous compartment and provide the typical ultrasound image of an Asian eye (see Figure 18.5c).[25]

Anterior and posterior accessory veins are often identified in the thigh (see Figure 18.6). These veins are often incompetent and receive reflux from the saphenous vein.[19]

Varying patterns of reflux through the different components of the SFJ and GSV system have been documented. Classification of abnormal, refluxing venous patterns has been a difficult task because of the anatomic variability of the vascular structures involved. In 2005 a panel of experts proposed a new classification of Great Saphenous vein reflux. This classification is shown in Figure 18.7.[26,27]

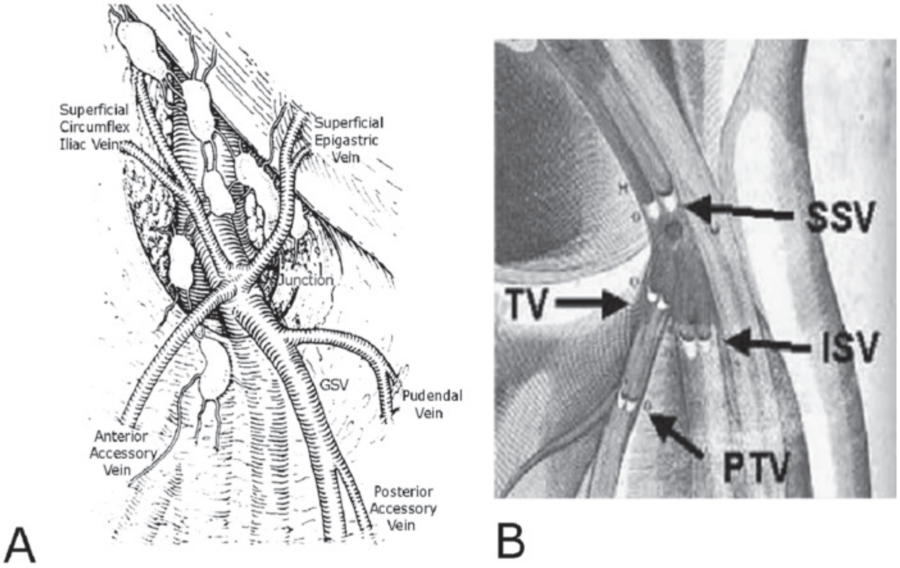


FIGURE 18.4 **A**. The saphenofemoral junction includes the Great Saphenous vein, the superficial iliac circumflex, the superficial epigastric, and the pudendal veins. **B**. Illustration of the SFJ with its valves. Modified from the *De Venarum Ostiolis*, of Jeronimus Fabricius Ab Acquapendente, Venice, 1603. *TV*, terminal valve; *PTV*, preterminal valve; *SSV*, suprasaphenic valve; *ISV*, infrasaphenic valve. (Adapted from Caggiati et al.[25])

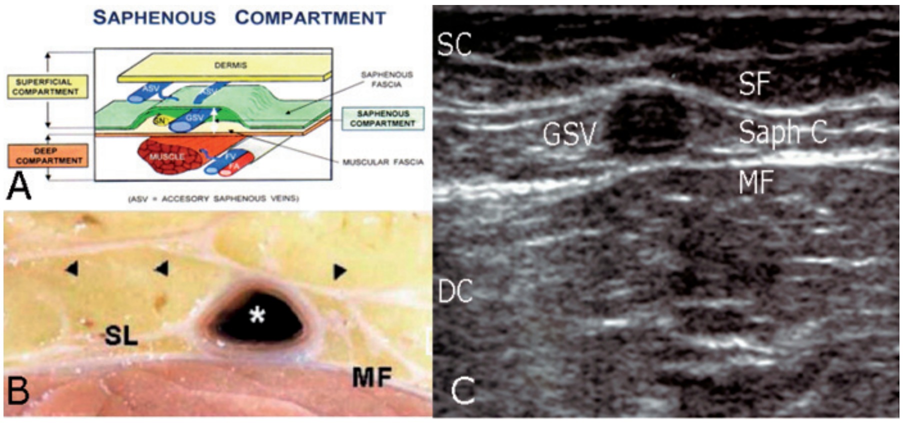


FIGURE 18.5 **A**. The saphenous compartment (SaphC) is bound superficially by the saphenous fascia (SF) and deeply by the muscular fascia (MF). It contains the saphenous veins (SV) and the saphenous nerve (SN). The accessory saphenous veins (ASV) lie external to this compartment, close to the dermis (D). *SC*, superficial compartment; *DC*, deep compartment. (Adapted from Reference 19.) **B**. Axial section from a cadaveric limb. The Great Saphenous vein enclosed in the saphenous compartment is clearly visualized. *MF*, muscular fascia; *SL* saphenous ligament. (Adapted from Reference 25.) **C**. Sonography of the Great Saphenous vein at mid thigh. The hyperechoic saphenous fascia (SF) and muscular fascia (MF) define the saphenous compartment in which the Great Saphenous vein courses.

Diameters of the GSV at several levels should always be recorded. The term superficial venous aneurysms has been proposed for segmental dilations of the GSV and Small Saphenous vein (SSV).[28] The term *varicosities* refers to more elongated and dilated superficial veins, such as the accessory saphenous veins (see Figure 18.8). The level, distance from the heel pad or floor, and antero-posterior and latero-lateral diameters of venous aneurysms should be recorded.[28]

In the leg, anterior and posterior arch veins can ascend parallel to the GSV (see Figure 18.6).[19]

Inter-saphenous veins are often present as communications between the GSV and Small Saphenous vein (SSV).

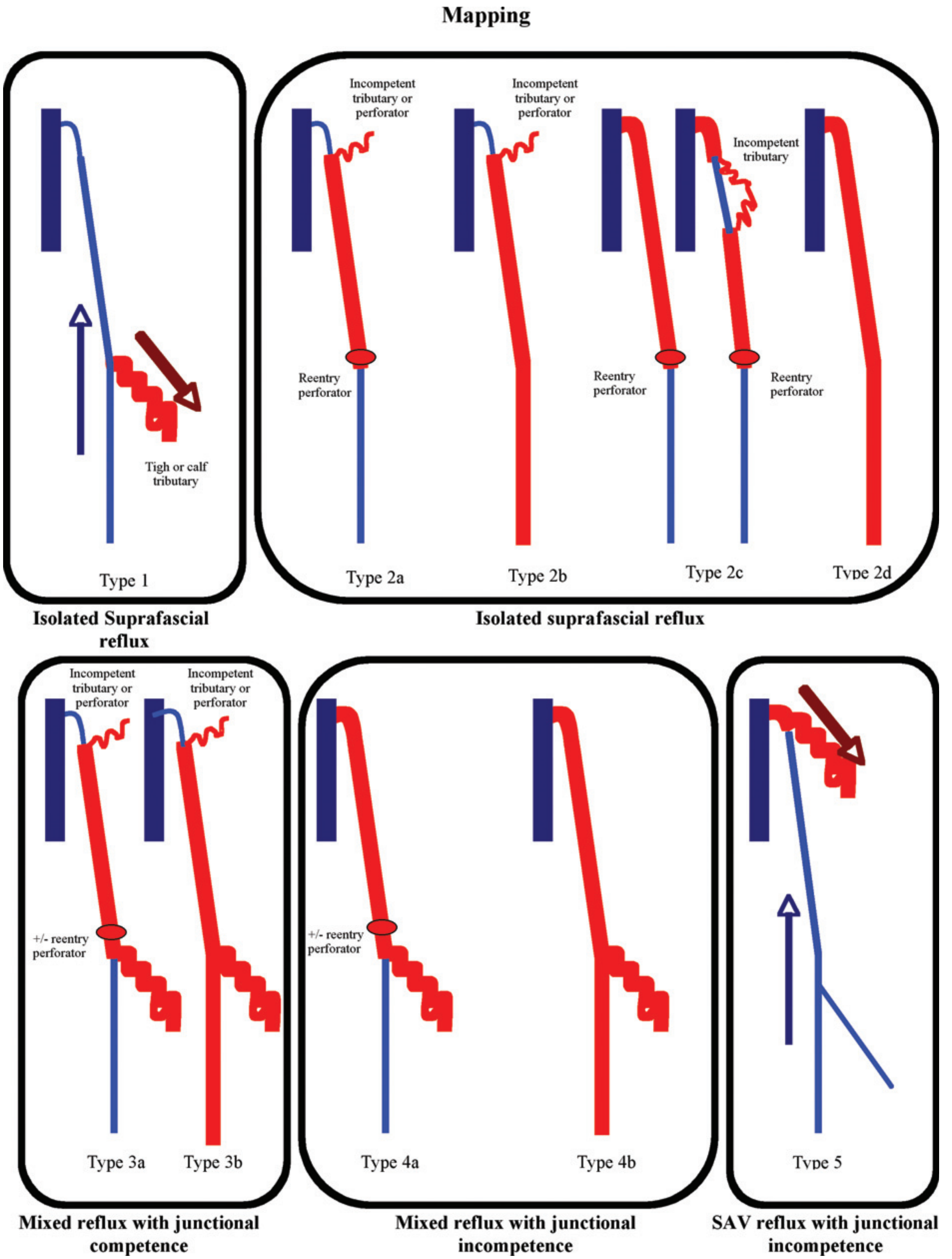
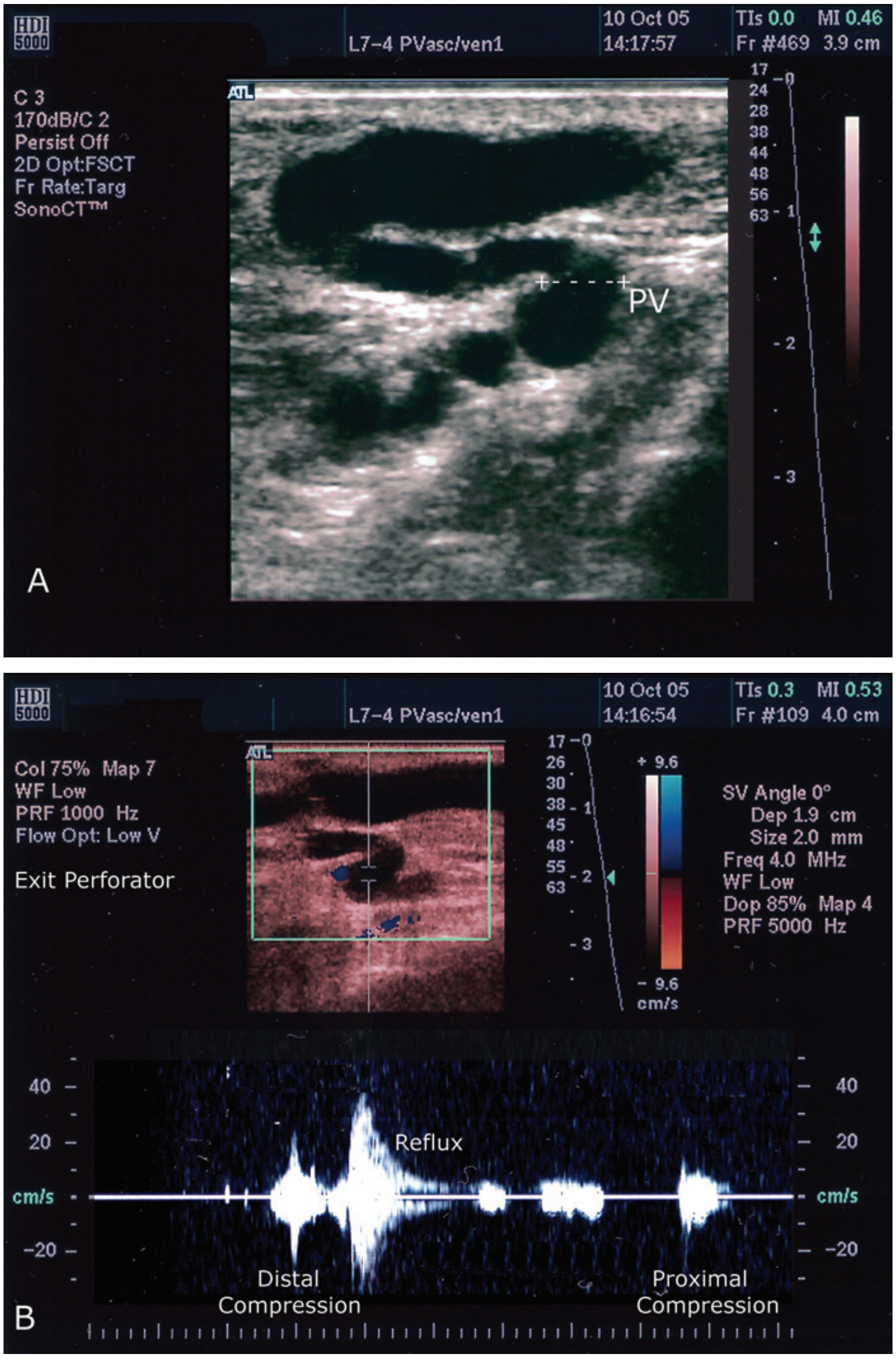


FIGURE 18.6 In 2005, a panel of experts proposed a new classification to be used in a prospective multicenter study testing the A.S.V.A.L. (selective ablation of varicose veins in local anesthesia) method. The classification reports five major types of saphenofemoral reflux. The recognition of each of them can guide different therapeutic approaches, such as the A.S.V.A.L. (Adapted from Pittaluga et al.[26,27])



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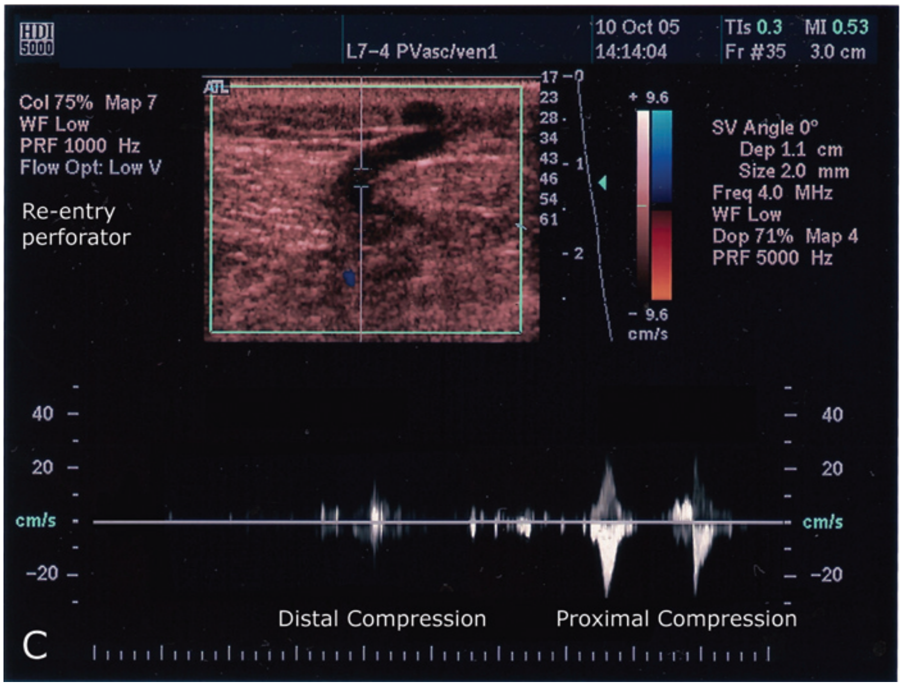

FIGURE 18.7 *Continued*

THE SMALL SAPHENOUS VEIN

The study of the SSV starts at the popliteal fossa by identification of the Sapheno-popliteal junction. Compression-release of the calf provides information concerning junctional reflux. The cranial extension of the SSV also can be identified between the biceps femoris and semimembranous muscles.[19] The Vein of Giacomini is another a cranial extension of the SSV that connects with the GSV in the posterio-medial aspect of the thigh.[19] In the calf, the SSV courses within a duplication of the superficial fascia similar to the GSV in the saphenous compartment.[19]

Throughout the entire examination, compression-release maneuvers serve to elicit reflux in the various venous segments.

PERFORATING VEINS

Perforator veins (PV) penetrate anatomic layers (see Figure 18.9). Communicating veins, such as intersaphenous veins, connect veins within the same anatomic layer.[19]

One of the innovations of the new *Terminologia Anatomica* of the venous system of lower limbs is the complete elimination of eponyms such as the Boyd, Sherman, and Cockett perforators. Descriptive terms designating location have been adopted.[19] A classification of them is shown in Table 18.3. No doubt, all the eponyms will persist.

During the examination, the location of each perforator is recorded by measuring its distance (in cm) from the floor. The diameter (in cm) of each perforator should be recorded.

Reflux is assessed by manual compression and release maneuvers. Blood flow direction and duration following the compression must be noted.

It has been suggested that an outward (toward the superficial veins) blow flow of duration greater than 350 ms, following manual distal compression, defines a perforator vein as incompetent.[6]

Perforators can be distinguished as exit and reentry veins. Exit veins are refluxing perforators usually associated with clusters of varicose veins and/or important skin changes, such as hyperpigmentation.[6]

Reentry perforators usually are found distal to major varicose veins and clusters. Their blood flow direction is inward (toward the deep veins) and they are not pathologic but merely competent.[6] Skin changes are not seen adjacent to reentry perforating veins.

Incompetent perforators usually are observed at the medial thigh, middle and distal third of the leg, and mid third of the calf.[6,13]

Scanning of the lateral aspect of the lower limb also is recommended. The lateral venous system that is seen on the lateral aspect of the thigh and the leg can show varicosities and important exit and reentry perforators. These are not as well characterized as the medial perforating veins.

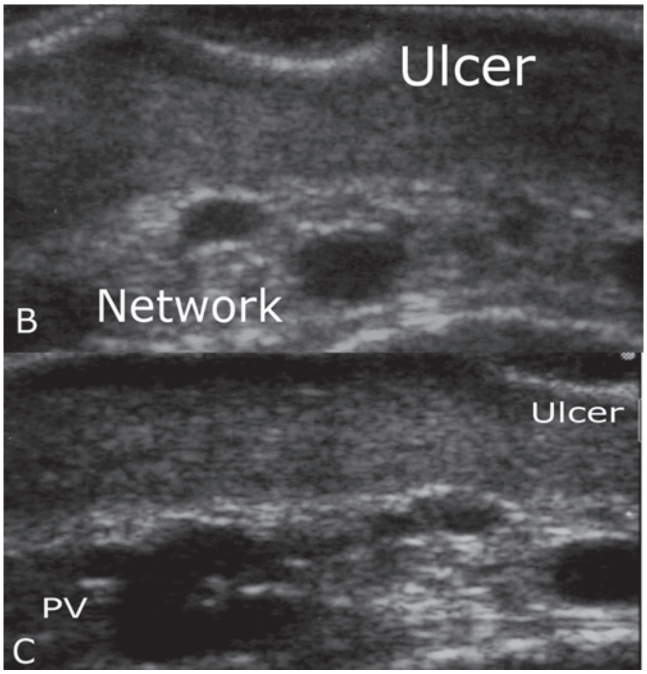

FIGURE 18.8 Perforating veins penetrate anatomic layers (**A**). Distal manual limb compression rather than proximal (**B** and **C**) elicits reflux in PVs.[35] Reflux is measured on the release phase of the augmentation maneuver and it is detected as outward flow (**B**) whose duration is greater than 350 ms in incompetent exit perforators.[6] Reentry perforators show little or absent outward flow following distal compressions (**C**).

TABLE 18.3 Perforating Veins[19]

Main groups	Subgroups
Foot perforators	Medial foot PV
	Lateral foot PV
	Plantar foot PV
	Dorsal foot PVs or intercapitular veins
	Plantar PV
Ankle Perforators	Anterior Ankle PV
	Medial Ankle PV
	Lateral Ankle PV
Leg Perforators	Medial Leg PV
	Paratibial PV
	Posterior Tibial PV
	Anterior Leg
	Lateral Leg
	Posterior Leg
	Medial Gastrocnemius
	Lateral Gastrocnemius
	Intergemellar PV
	Para-achillean PV
Knee Perforators	Medial Knee PV
	Suprapatellar PV
	Lateral PV
	Infrapatellar PV
	Popliteal Fossa
Thigh Perforators	Medial Thigh PV
	PV of the femoral canal
	Inguinal PV
	Anterior thigh PV
	Lateral thigh PV
	Posterior Thigh PVs
	Pudendal PV

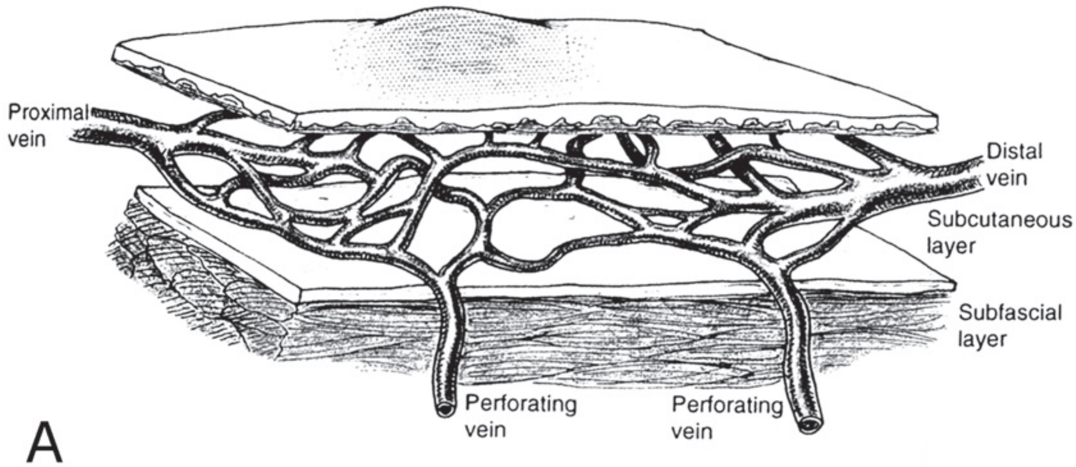

FIGURE 18.9 A network of varicose veins and incompetent perforators is often identified in the vicinity of venous ulcers usually beneath the ulcer (**A**).[31]

TABLE 18.4 Major Interrogation Points for Venous Reflux Examination[14]

Interrogation points	
Femoral Vein	Small Saphenous Vein
Saphenofemoral Junction	Intersaphenous Veins
Great Saphenous Vein	Medial Thigh PVs
Accessory Veins (anterior and posterior)	Leg PVs
Arch Veins (anterior and posterior)	Ankle PVs
Popliteal Vein-Gastrocnemius Veins	

ULTRASOUND MAPPING OF VENOUS ULCERS

Venous ulcers usually are associated with varicose veins and refluxing perforators located in the immediate vicinity of the ulcerated area. A superficial network of enlarged and dilated veins often can be observed underneath the ulcer (see Figure 18.8).[29] The description and the documentation of reflux in these veins can help to indicate a particular therapeutic approach.[29–31]

DEEP VEINS

The ultrasound examination also must include the deep veins. Femoral and popliteal veins usually are studied with the patient in supine position.[32] Patency is assessed by distal compression. Irregularities of the vascular wall may appear as hyperechoic areas and always should be noted in patients with superficial reflux and a clinical history suggestive of previous deep vein thrombosis or pulmonary embolism. Sural, anterior tibial, posterior tibial, and peroneal veins are imaged while the patient is in the sitting position, usually starting from the ankle and proceeding toward the knee.[32] Compression and flow augmentation maneuvers assess their patency and presence of reflux. Deep vein abnormalities must be recorded.

DISCUSSION

Duplex ultrasound sonography represents the best choice in evaluation of venous reflux in lower limbs.[6,8,13] This test is noninvasive, generally acceptable to the patient, and inexpensive. It provides direct imaging, localization, and extent of venous reflux with a surprisingly high sensitivity (95%) and specificity (100%).[33]

Duplex ultrasound findings correlate with the angioscopic observation of incompetent vein valves in advanced chronic venous insufficiency.[34] As demonstrated by Yamaki et al., high peak reflux velocities (>30 cm/s), reflux duration greater than 3 s, and an enlarged valve annulus measured by duplex ultrasonography at the SFJ are closely related to angioscopically deformed and incompetent terminal valves (Type III and Type IV valves).[34]

In contrast, duplex ultrasound PV identification and characterization have shown to be more difficult and less accurate.[33] Lower sensitivity rates (51%) have been reported when the number of perforators identified by ultrasound, ascending phlebography (AP), and subfascial endoscopic perforator surgery (SEPS) were compared.[33]

CONCLUSION

Duplex ultrasound sonography is the optimal diagnostic modality for assessment of lower extremity reflux. Insights into pathology, proper technique, and uniform testing are essential.[13] A clear graphic notation of significant vein diameters, anomalous anatomy, superficial venous aneurysms, perforating veins, and presence and extent of reflux should always be recorded during the examination. The most important interrogation points for the venous reflux examination are indicated in Table 18.4. These serve as basic guidelines because the interested vascular ultrasonographer must trace out duplicated veins and note reflux in major tributaries, such as the accessory veins.

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CHAPTER

19

Conventional Sclerotherapy versus Surgery for Varicose Veins

T.R. CHEATLE

Many clinicians who treat varicose veins will take issue with the title of this chapter. The two techniques, it will be said, are complementary, not mutually exclusive, alternatives. In addition, what about foam sclerotherapy? VNUS closure? Endovenous laser ablation? Powered phlebectomy? Surely, with these exciting new treatments becoming available, the title smacks of a man comparing smoke signals to carrier pigeons in the age of the telephone.

Of course the two techniques are indeed complementary, but it is still reasonable to find out which gives the better results (however one measures "better") in the average patient. As far as newer techniques go (many dealt with in other chapters herein), we do not yet know what the long-term results of treatment will be. And for the average practitioner in many countries, they will not be readily available, either due to expense, lack of ability to become trained in them, or a variety of other reasons. Thus for many doctors, the realistic choice they face in treating patients with varicose veins remains between surgery or conventional sclerotherapy—at least for the time being.

The history of injection sclerotherapy is summarized by Browse et al.[1] The elaboration of the technique and indications for its use were expounded first by Karl Sigg of Basle, Switzerland,[2] and subsequently, and perhaps most influentially, by George Fegan of Dublin, Ireland.[3]

Sigg is one of the major figures in the development of compression sclerotherapy. The technique of inserting the needle with the patient in the standing position but injecting with the leg horizontal is attributed to him. He also recommended starting sclerotherapy in the most distal varices, as opposed to Tournay who had recommended starting at the most proximal point of reflux. In addition he was among the first to stress the desirability of graduated compression rather than uniform compression. For these innovations as much as for his enthusiastic and detailed publications, he is remembered as one of the founders of modern sclerotherapy.

George Fegan's name has become synonymous with the use of sclerotherapy in many parts of the world. He makes the point strongly that the aim of sclerotherapy is not to cause thrombosis in a varix, but rather to cause an obliterative fibrosis. Histological evidence is adduced to show the recanalization that occurs when a vein has been merely thrombosed, compared to the absence of same when fibrous obliteration has been achieved. This obliteration is obtained by immediate and continuous compression, sustained for six weeks. Great importance is laid on the technique of bandaging.

Fegan's papers are essentially descriptive and do not purport to be trials. Clearly, as his results show, he was an expert and dedicated exponent of the method he developed. His emphasis on using an "empty vein" technique, the importance he placed on controlling points of reflux (especially the Hunterian perforator above the femoral condyle) rather than simply injecting varices at random, and his bandaging technique have all formed the basis of most sclerotherapy done in many parts of the world today.

Stripping the Great Saphenous vein has been practiced since the description by Keller in 1905,[4] and the subsequent century, it is fair to say, has produced only modest modifications of the principles of varicose vein surgery established before the first world war.

Given that both surgery and sclerotherapy have been practiced for so long, it is very disappointing that so little high quality literature exists to compare the two techniques. Papers on phlebological topics have not always conformed to the highest standards of scientific rigor and have too often relied on anecdotal or retrospective accounts of outcome. The number of useful randomized trials comparing the two

methods is very small, and most of these were performed and published more than a generation ago.

John Hobbs made one of the first attempts to compare in a scientific way the outcome of the two techniques.[5] In the key part of his paper, 500 patients with varicose veins were randomized to either surgical or injection treatment. The patients were photographed and classified by severity before treatment. However, no data are given as to the pathophysiology in these patients, for example, Great or Small Saphenous incompetence. Injection treatment was performed using Hobbs' own method, which involves inserting the needle and injecting with the patient flat. Three percent Sodium Tetradecyl (STD) was used, and an average of 11.4 injections per leg were given. The legs were bandaged for six weeks. A minor flaw in the study was that those allocated to surgery were treated by a number of different surgeons, presumably of differing experience and ability, although Hobbs states that "most" of the operations were done by him. The patients were seen and reassessed at six-month intervals for up to six years, and classified as either cured, improved, or failed, according to the less favorable view of either patient or surgeon.

Hobbs found that after one year, patients treated by sclerotherapy had a better result than those operated upon. However over subsequent years, this difference disappeared and was reversed due to increasing numbers of recurrences seen in the injection group. This was despite intermittent extra injection treatments given to patients in the sclerotherapy group. By six years, approximately 20% of the surgical group were classified as failures, compared with almost 70% of the sclerotherapy group. Hobbs concluded that patients with definite saphenofemoral or popliteal reflux were best served by surgery, whereas those without should get sclerotherapy; a view that would be accepted widely by many vascular surgeons practicing today.

Two papers from Chant's group[6,7] give the results of another randomized controlled trial in which 115 patients were treated with compression sclerotherapy and 100 treated by surgery. Again, we do not know how many had Great or Small Saphenous incompetence, or neither. Ninety patients were excluded from the trial because they either had recurrent or trivial veins or had medical or social contraindications, or because they expressed a strong preference for one form of treatment.

Surgical treatment consisted of saphenofemoral or saphenopopliteal ligation, stripping of the Great or Small Saphenous vein, and ligation of any clinically detected perforators. Injection sclerotherapy was performed using Fegan's method. Information concerning the number of injections given and the number of sessions used is not given.

The patients were followed up at six months and at yearly intervals thereafter. The first paper was written when 93% had achieved a three-year follow-up. Patients were classified depending on their requirement for further treatment, be it surgery, sclerotherapy, or stockings. Including those who declined any treatment after randomization, the authors found that 25% in the surgical group had required further treatment compared to 27% in the group treated by compression sclerotherapy. On these results the authors concluded that the two treatments were equivalent in their effect. They also made the point that sclerotherapy was often more acceptable to women with children, as it avoided a disruptive hospital admission, even if several outpatient visits were required.

In their second paper, the same patients were reviewed, having now been followed up for a minimum of five years. At this stage 40% of those initially treated by sclerotherapy had required some form of retreatment compared to 24.2% of those treated surgically. Interestingly, the authors found that difference was principally in older patients; in those aged less than 35, the two treatments remained equivalent. The results of this paper indicated a long-term advantage to surgical treatment, although the scale of the difference in results is quite small.

In John Seddon's 1973 paper,[8] 201 patients with demonstrable incompetence of the saphenous systems and/or ulceration due to perforator incompetence were studied. They were divided (presumably randomly, though the paper does not say this) to receive either surgical treatment (saphenofemoral disconnection with stripping of the Great Saphenous vein and perforator ligation) or sclerotherapy by Fegan's method. Patients undergoing sclerotherapy were reviewed every three weeks until treatment was deemed complete; the average number of injections was not given. Posttreatment compression was applied using bandages, though the duration is not stated.

Follow-up was between 12 and 18 months in all cases. Twenty-nine of the 149 limbs (19%) treated by sclerotherapy either did not respond to treatment (3) or had residual (19) or recurrent (7) veins at follow-up. This compares to 25 of 125 limbs treated surgically (20%). Two of the 15 patients with ulcers in the sclerotherapy group suffered ulcer recurrence, compared to none of the five treated surgically. A small number of minor complications occurred in both groups.

The author concludes that the outcome of the two treatment methods is approximately the same. This agrees with the findings of other studies for the follow-up period described, but whether that equivalence would have been maintained over a longer period is a moot point; the studies of Hobbs and Chant described earlier would suggest not.

Motivated largely by the length of time patients were staying in hospital following varicose vein surgery (10.5 days), Doran and White[9] designed a trial to compare surgical treatment to sclerotherapy. Five hundred and two limbs in 331 patients with primary uncomplicated varicose veins were randomized (by year of birth) to receive either sclerotherapy by Fegan's method (280 limbs) or conventional surgery (222 limbs). No details of exactly what

operations were performed are given. Sixty-four point six percent of patients in the sclerotherapy group had between one and five visits, with never more than four injections being given at a time; 23.8% had between six and 10 visits, and 11.6% had over 10 visits. Outcome was measured at one and two years simply by ascertaining whether patients had required further treatment (i.e., injections) or not. Subjective or objective evaluation of the limbs is not described.

At the end of one year, 24.2% of limbs in the sclerotherapy group had required further treatment, compared to 44.8% in the surgical group. After an additional year's follow-up, another 21.3% in the injection group and 16.4% in the surgical group had received further treatment although, as the authors admit, the high drop-out rate by this stage (about one third) made these results of uncertain significance.

The authors conclude that "the initial response of varicose veins is better if Fegan's method is used than if they are operated upon."

This is the only randomized trial to come down in favor of sclerotherapy over surgical treatment. Unfortunately there appear to be too many flaws in the study to warrant its rather grand title. The follow-up period is too short; other studies agree that after one year, results of the two forms of treatment may be similar, but that the recurrence rate rises in the injection group therafter. The requirement of almost half the surgically treated group to have injection sclerotherapy within a year of operation is troubling. As mentioned, we do not know what operations were done, but this figure suggests that the surgeons involved may have been less than assiduous in their performance of multiple avulsions. The method of deciding whether treatment has failed or not seems intrinsically unfair; patients receiving sclerotherapy can go on doing so at weekly intervals for an indefinite period until the clinician is satisfied, whereas surgical patients needing, perhaps, just one or two post-operative injections are classed as treatment failures.

The paper confirms that skilled sclerotherapy is an effective treatment for varicose veins in the short to medium term, but cannot be said to have shown it to be a superior treatment to surgery.

Jakobsen's 1979 paper[10] counts as one of the key papers on the subject by being one of the very few studies to compare directly surgical and sclerotherapeutic treatment. However it suffers in its subjective method of classification and assessment. Through no fault of its author, it was written a few years before Doppler examination and duplex ultrasound became standard objective methods of assessment of venous abnormality.

Some 516 patients who presented with saphenous varices were stratified to one of three treatment groups. It is unclear whether this was a randomization or not. The three groups comprised 161 patients who had radical surgery—junctional ligation with excision of the Great and/or Small Saphenous vein, 165 patients who had junctional ligation under local anesthetic combined with sclerotherapy, and 157 patients who had sclerotherapy alone (Sigg's method). No information is given concerning the number of treatment sessions or number of injections per session in the sclerotherapy group.

Patients were followed up at three months and at three years. Their outcome was classified both objectively and subjectively. Results for all treatments were, broadly speaking, very good at three months but differences were demonstrated at the three-year follow-up. By objective evaluation, 89.8% of patients undergoing radical surgery had satisfactory results, as had 65.2% in the local surgery + sclerotherapy group. Only 36.6% of those having sclerotherapy alone were classified as objectively satisfactory at three years. Interestingly, the patients' subjective evaluations of their outcome showed less striking differences, with 93%, 84.8%, and 70.5%, respectively, reporting that they were satisfied with the results at three years. The authors conclude that radical surgery is the best treatment for varicose veins.

The most recently published of the very few randomized trials comparing surgery with sclerotherapy is by Einarsson et al.[11] One hundred and sixty-four patients with symptomatic primary varicosities were randomized to either operative treatment or compression sclerotherapy (CST). Patients were assessed clinically and by foot volumetry before treatment. Eighty patients underwent surgery and 84 had CST. They were well matched for age, sex, and pattern of venous disease. The type of surgery was determined by the clinical diagnosis (e.g., Great or Small Saphenous incompetence) and the presence or absence of perforating vein incompetence. Sclerotherapy was performed by Hobbs' modification of Fegan's technique. An average of five injections per patient was given, over either one, two, or three sessions. Patients in both groups had four to six weeks of posttreatment compression.

Patients were followed up at six months, one year, three years, and five years. They were assessed by clinical inspection, subjective opinion of the patient, and by foot volumetry. Follow-up compliance was reasonably good, with 78% (CST) and 76% (surgery) attending for the full five-year follow-up.

At one year, 97% of surgical patients and 82% of CST patients considered themselves cured or improved. The physician's assessment was 93% and 80%, respectively. The results in the CST group fell away over the following four years. By five years, 95% of surgical patients still considered themselves cured or better, compared with only 45% in the CST group. Objective assessment gave figures of 90% and 26%, respectively. The foot volumetry results, measuring expelled volume (a measure of calf muscle function) and refilling flow (a measure of reflux), gave broadly similar results. Ten percent of operated patients had problems with sural or saphenous nerve damage, whereas 22% of CST

patients had problems with superficial thrombophlebitis. Most of this was minor, but five patients required surgery because of phlebitis in the long saphenous vein and were thus classified as failures.

This seems to have been a well-conducted trial, the results of which support those of Hobbs and Jakobsen. The trial started just before duplex scanning became generally available, but foot volumetry is a valid method for assessing calf muscle function and refilling times and has been shown to correlate well with direct venous pressure measurements. However the average number of injections[5] given to patients in the sclerotherapy arm of the trial seems remarkably small, leading to the inevitable question as to whether more assiduous treatment in this group might not have led to a better outcome. In addition, the high rate of postinjection superficial thrombophlebitis suggests that the empty-vein technique required by Fegan may not always have been achieved.

Two further trials warrant mention, although neither can be considered as seminal as those described earlier. A multiauthor (31 authors), multicenter trial covering 10 years has been reported[12] in which patients were randomized to receive one of six treatment regimens: sclerotherapy, high-dose sclerotherapy, multiple ligations, stab avulsions, foam sclerotherapy, and ligations + sclerotherapy. A variety of clinical and laboratory-based endpoints were used. After 10 years, no clear differences in outcome could be identified and all treatment modalities were considered to be of broadly equal efficacy. It is difficult to draw clear conclusions from this paper, and the absence of a group treated by standard surgery—long saphenous stripping with flush SFJ ligation and multiple avulsions—would seem to be an opportunity missed.

A Dutch paper from the same year[13] compared simple phlebectomy to sclerotherapy in 98 limbs. A clear advantage for phlebectomy at two years was demonstrated.

Another paper of interest compared stripping the Great Saphenous vein to a combination of high saphenofemoral ligation and sclerotherapy of the varicosities.[14] One hundred and eighty-six limbs with proven isolated saphenofemoral incompetence were randomized to one treatment or the other. After three years, there was a clear advantage for the group who had undergone stripping, both subjectively and objectively, although a very high (33%) frequency of saphenous nerve damage was reported in this group. However this study is not really comparable to those described earlier since neither patient group underwent sclerotherapy alone.

Also of interest is the paper of Brethauer et al.,[15] in which service personnel or members of their families underwent saphenofemoral ligation and perforator ligation combined with either stab phlebectomies or sclerotherapy. The two groups were not randomized and the follow-up period is quite short (mean follow-up time = 418 days), so the results must be treated with caution. However, it is of interest to find that there was no difference in outcome or patient satisfaction between the two groups, but that the surgical group had their treatment completed in a shorter period of time.

Three further publications from the last decade must be mentioned—a consensus document, a questionnaire of current practice, and a Cochrane review.

The first[16] summarizes the proceedings of three consensus conferences held in Padua (twice) and Venice in 1994 and 1995. Thirty-one participants (all but one European) and eight further participants (six from outside Europe) met to answer the question: Is sclerotherapy effective and, if so, under what circumstances? Participants and contributors were acknowledged experts, invited by nomination from national phlebological societies. It was felt that personal experience was of greater importance in this area than many others in medicine, since the low scientific standard of many phlebological publications made an evidence-based approach difficult. A questionnaire was sent to over a thousand phlebogists worldwide in order to reveal current practice in the field of sclerotherapy.

It was agreed that sclerotherapy is the treatment of choice for small varicose veins. Unfortunately the term "small" is not defined but includes telangiectasia and reticular veins.

For larger veins not arising from an incompetent saphenous trunk, it was agreed that sclerotherapy was an adequate treatment, though there appears to have been some dissent about its role in treating incompetent perforating veins.

No consensus could be reached on whether or not varicosities arising from an incompetent Great Saphenous vein should be treated by sclerotherapy. It was agreed that veins arising from an incompetent Small Saphenous system could be treated by either surgery or sclerotherapy, but it was felt that there was inadequate evidence in the literature to give any recommendations on this point.

Agreement was reached that the following circumstances constituted absolute contraindications to the use of sclerotherapy: allergy to the sclerosing agent, severe systemic disease, recent DVT, infection, inability to walk, and severe arterial disease. Most of these would, of course, also constitute contraindications to surgery.

The participants highlighted the shortcomings in the small number of randomized controlled studies that have been reported. The discrepancies between the excellent results of personal series and those of randomized trials is also pointed up. The participants agreed that it was impossible to say whether or not sclerotherapy prevented complications of varicose veins. In future studies, the following outcome measures were suggested: prevention and treatment of complications, patient satisfaction, reattendance, lack of effect, side effects, recurrence of varicose veins, and cost. An ideal study was proposed, which would have the following characteristics:

1) Prospective, randomized, controlled.
2) Homogenous patient sample; for example, all long saphenous vein varicosities. Preprocedure investigation would be mandatory to ensure this.
3) Standardized sclerotherapy technique.
4) All complications and side effects of treatment to be recorded.
5) Independent assessment of objective criteria when measuring outcome.
6) At least five years follow-up, with full details of all subsequent treatment.

This paper is a thorough and honest attempt to reach clear recommendations about the practice of sclerotherapy in venous disease. Unfortunately, perhaps inevitably, the consensus recommendations are so unexceptional as to be anodyne. This may be due to the large number of participants but more importantly reflects the poor quality of the literature available, which the authors recognize. It is disappointing that instead of making suggestions about how to find out which technique of sclerotherapy works best, the authors make the rather bland suggestion that it is left to individual clinicians to use the method they like best. The most useful part of the document is the outline of the ideal study in examining the efficacy of sclerotherapy, which should act as a model for future investigators.

A subsequent paper[17] described the results of a study in which 350 members of the Vascular Surgical Society of Great Britain and Ireland were contacted by post and asked about the place of venous sclerotherapy in their practice. They were also asked whether their use of the technique was increasing or decreasing with time.

Two hundred eighteen (62%) replied: 18.3% never used sclerotherapy; only 4.6% used it when the patient was known to have proximal junctional incompetence; 69.7% used it when such incompetence was absent; 77% used the method to treat residual varices left behind after operation; 64.7% used it to treat recurrent varices without junctional incompetence.

The median compression time was less than that usually recommended by the inventors of the technique. The median time after sclerotherapy for varicose veins was two weeks, whereas after sclerotherapy for telangiectasia it was only four days.

The trend was for surgeons to use sclerotherapy less frequently for varicose veins than formerly, but more often for telangiectasia.

One important point coming out of this study was that only 33% of respondents both used sclerotherapy and had a specialized varicose vein clinic. Clearly, this limits the scope for training junior surgeons. Lack of proper training may lead to poor technique, and this may contribute to what some would see as an ongoing underuse of the method.

Perhaps the most important publication of recent times on this topic has been the 2004 Cochrane Systematic Review,[18] which set out to examine the evidence concerning the question suggested by the title of this chapter. The authors searched 13 databases, contacted health economics agencies and guideline producing agencies, examined trial registers, and in general did everything possible to ensure all relevant data were included in the review. Only nine randomized trials were identified and the variety of outcome measures and classification systems meant that the authors felt unable to draw firm conclusions or make recommendations. They commented that there was a trend for early results to favor sclerotherapy but, after a follow-up period of two to three years, for this trend to be reversed in favor of surgery. Insufficient data on costs prevented a cost-effectiveness recommendation being made either.

These papers give a snapshot of current feeling about the use of sclerotherapy. The majority of trials that compare surgery with sclerotherapy for primary varicose veins indicate that the results are similar over the medium term, but that in the long term, surgery is more durable, with fewer recurrences. Whether this matters all that much can be debated. In a level-headed editorial on the topic,[19] Guex and Isaacs argue that recurrence is not a disaster "as if venous reflux were akin to cancer" and that the need for reinjection may still represent an acceptable outcome. Clearly, the prospect of a "once and for all" treatment, with two weeks off work and a small risk of surgical complications will be appropriate to some patients, but for others a less invasive procedure, avoiding anesthesia, but with an increased likelihood of eventual reintervention will be preferable. There is no right answer.

Most vascular surgeons agree that sclerotherapy is the treatment of choice for thread veins, and use the technique for these and for residual or recurrent veins after definitive surgery.

One problem that occurs in comparing surgery to sclerotherapy is that the latter, especially, is dependent on the degree of skill and commitment with which it is applied. Whereas stripping the long saphenous vein is basically an all-or-nothing procedure, the outcome of which is likely to be much the same whether it be done smoothly or clumsily (within limits!), the same cannot be said of injection treatment. Inexpertly performed sclerotherapy is likely to lead to very poor results and many complications. Thus committed advocates of the technique, who spend a great deal of time and concentration in using the method, are likely to get better results than those who view it as an inferior treatment and use it reluctantly. The argument that papers that report poor outcomes following sclerotherapy do so because the injections were done improperly, or insufficiently, or with inadequate compression, is always going to be difficult to counter, and may well, of course, have some truth in it.

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C H A P T E R

20

Sclerotherapy and Ultrasound-Guided Sclerotherapy

PAUL THIBAULT

SCLEROTHERAPY

Varicose veins are a degenerative disease of the venous system where there is a defect in the strength of the vein wall with associated valvular dysfunction resulting in reflux (reverse) flow in affected areas of the superficial venous system of the legs. Usually reflux from the deep to superficial system through incompetent venous junctions and perforator veins is a major contributor to the superficial venous insufficiency. Because venous disease is a chronic disease, treatment usually is directed at controlling the disease rather than curing it. It is therefore important that interventional treatment does not aggravate the condition in the long term.

Sclerotherapy refers to the method of treating varicose veins, where a foreign substance, usually a chemical, is introduced into the lumen of a vein to cause endothelial necrosis and subsequent fibrosis of the vein. Apart from reducing the size of the vein to a small fibrous cord, effective sclerotherapy also eliminates the physiopathological reflux associated with varicose veins. As such, sclerotherapy is an alternative treatment to surgery and other physical endovenous ablation techniques such as endovenous laser (EVL) in the management of varicose veins. Sclerotherapy differs from the other ablative techniques in that it can be effective treatment for all types of pathological venous dilatations from major truncal varicose veins to the finest telangiectases.

Sclerotherapy for varicose veins associated with Great Saphenous vein (GSV) and Small Saphenous vein (SSV) incompetence traditionally has been relegated to treating residual varicose veins following surgical stripping or varicose veins associated with isolated perforator vein incompetence.[1] Apart from a relatively brief period of popularity of the Fegan method of sclerotherapy in the 1960s and early 1970s, surgical methods generally have been accepted as having a significantly better long-term recurrence rate compared to sclerotherapy. This has been thought to be due to the fact that traditional sclerotherapy was unable to control the proximal source of reflux—usually the saphenofemoral (SFJ) and saphenopopliteal (SPJ) junctions—adequately. In addition, preultrasound methods of sclerosing the GSV have been shown to be relatively ineffective. Some methods such as the Cloutier technique administered a single "blind" injection of a major sclerosing agent a few centimeters below the SFJ, repeated every seven to 21 days until the GSV was occluded. Such methods have been openly discouraged as creditable methods of treating GSV or SSV incompetence because they were thought to have an inheritantly high risk of damaging the deep venous system or of inadvertent intraarterial injection.

Duplex ultrasound has become the gold standard in the investigation of lower limb venous disease. As an independent investigation, duplex scanning has unrivalled relevance in the clinical decision-making process as well as being used in the serial assessment of disease progress and effectiveness of treatment. Ultrasound guidance of sclerosant injections is a logical extension of the pretreatment evaluation and gives sclerotherapy the potential to rival other ablative methods in effectiveness in the treatment of varicose veins.

HISTORY OF ULTRASOUND-GUIDED SCLEROTHERAPY (UGS)

The method of ultrasonic guidance of injection into the superficial venous system was first published in 1989.[2] The method initially was used for treatment of incompetent

saphenous axes and in 1992 the method of injecting incompetent perforating veins associated with postsurgical recurrences was described.[3] Medium-term results of SFJ incompetence treated by UGS were reported by Kanter and Thibault in 1996.[4] In the late 1990s, several practitioners around the world began using sclerosant foam injected using ultrasound guidance, and the first medium-term results were reported by Cabrera in 2000.[5] Since that time UGS using microfoamed sclerosants has become the accepted method of UGS.[6]

PRETREATMENT ULTRASOUND MAPPING

Duplex venous scanning is the essential pretreatment investigation prior to either sclerotherapy or UGS of major varicose veins and truncal incompetence. Through duplex scanning, patterns of venous incompetence will be found to be extremely variable and often unexpected. Duplex scanning involves B-mode imaging of the deep and superficial veins combined with directional pulsed Doppler assessment of blood flow. Color-duplex imaging superimposes blood flow information onto the B-mode ultrasound image, permitting visual assessment of blood flow while creating an anatomical map of the venous anatomy. The details of venous duplex examination have been described in a previous chapter and will not be dealt with here.

In short, duplex examination is able to provide an accurate anatomical and physiological map of superficial and deep venous incompetence and localize points of reflux from the deep to superficial venous system. With duplex examination a detailed map of reflux paths in the superficial system, from the proximal origin of the reflux (usually from the deep system) to a distal reentry point, can be created. This map will allow optimal decisions regarding sclerotherapy intervention and will ensure that all significant areas of reflux are addressed by treatment and, conversely, that all normal veins are preserved.[7] Diameters of major veins and junctions are also recorded during the duplex examination. These measurements may influence various parameters of the treatment process including selection of sclerosing agent and foam, and postsclerotherapy compression.

Following the duplex examination, the treatment process then is directed toward eliminating all the incompetent superficial pathways mapped out with duplex ultrasound, and then in the posttreatment phase, reexamining with duplex to ensure that the reflux pathways have not recanalized prior to complete fibrosis of the vein that usually occurs between six to 12 months following initial treatment.

TECHNIQUES OF ULTRASOUND-GUIDED SCLEROTHERAPY (UGS)

Sclerosing Agents

Generally, only relatively strong sclerosants are used in UGS. In an international survey[8] of 44 phlebologists who were known to use UGS extensively, 95% used sodium tetradecyl sulphate (STS) (Fibrovein™; STD Pharmaceuticals, Hereford, England), and 5% used 3% polidocanol (POL) (Aethoxysclerol™; Kreusler Pharma, Wiesbaden, Germany). There was a small minority of phlebologists that used polyiodinated iodine as an alternative solution in particular circumstances, such as in the presence of allergy to STS or at deep to superficial junctions. With sclerosant concentration, generally 3% STS was used although some phlebologists use STS in various strengths from 0.75% to 2%.

In this survey, 34% of phlebologists used foamed sclerosants with STS again being the most common agent used as foam. It is likely that the ratio of phlebologists using foam sclerosants compared with solution foam has increased significantly since that survey, as the benefits of foam have become more widely known. The use of foam is described in more detail in another chapter.

In a recently published study,[9] STS and POL, in both solution and foam formulations were shown to have similar efficacy, tolerability, and patient satisfaction. There is good evidence, however, that POL is a weaker detergent type of sclerosant than STS[10] and higher concentrations are necessary to produce complete vascular sclerosis for any given diameter of vein (see Table 20.1).[11]

This is the most likely reason why the majority of phlebologists prefer STS when performing UGS, as in general, larger truncal veins are being treated with this technique.[6]

Patient Positioning

For treatment of veins on the medial aspect of the leg, patients are placed in the supine position with the treated leg level and externally rotated at the hip. The knee is usually

TABLE 20.1 Approximate Equivalent Concentrations of STS and Polidocanol Required for Effective Sclerosis of Increasing Caliber of Lower Limb Veins

Vein caliber mm	STS concentration %	Polidocanol concentration %
0.1–0.5	0.1	0.25
0.5–1.0	0.15	0.5
1.0–2.0	0.3	1.0
2.0–3.0	0.5	1.5
3.0–5.0	0.75	2.0
5.0–8.0	1.0–3.0	3.0–5.0

slightly flexed in order to relax all muscle groups. If small incompetent veins are being treated, the patient can be placed in the semireclining position in order to dilate the veins slightly, thereby assisting ultrasound visualization and subsequent injection. For treatment of veins on the posterior thigh or calf, the patient is positioned in the prone position with the foot supported by a pillow so that the knee is flexed slightly.[3] This positioning is important when injecting the SSV near the popliteal fossa, where the vein will be compressed if the knee is totally extended.

Closed Needle Technique

Materials

The needle size used can vary from 21 g to 25 g. The most common size used is 25 gauge 1½ inch (0.50 × 38 mm), because this is the smallest diameter needle that is readily visualized by B-mode ultrasound, and is long enough to reach most superficial veins from the point of skin penetration. Usually the sclerosant is drawn up into a 2 or 3 ml luer lock syringe. When microfoam is used, the Tessari method[11] will also require the use of a 5 ml Luer lock syringe to draw up air or other gas to form the microfoam.

Method

The closed needle technique is the most commonly used method.[8] With this technique, the needle is attached to the syringe containing the sclerosant at all times. A smaller proportion of phlebologists use an open needle technique (needle is removed to determine color/flow of blood). The procedure may be performed with the assistance of a vascular sonographer, or with the phlebologist performing both the ultrasound and the injections alone (solo technique).[8]

The initial injection usually is performed near to the proximal origin of the venous reflux.[4] A small proportion of practitioners inject more distally, then manually "milk" the sclerosant toward the proximal source of reflux using real-time ultrasound monitoring. Either way the final objective is to have the total segment of incompetent vein, from the proximal reflux point to the distal reentry point, uniformly filled with sclerosant foam. This can be observed with real-time B-mode ultrasound and will be accompanied by vasospasm of the treated vein.

The sonographer initially will localize the site of the vein to be injected in transverse view. The depth of the vein below the skin surface will be noted, as this will determine the angle of approach of the needle. The injection can then be performed either with the vein viewed in transverse section or in sagittal or longitudinal section. Approximately 50% of practitioners utilize the transverse approach solely, 33% the longitudinal approach solely, and the remainder use both approaches depending on various technical variables associated with each individual injection.[8] The transverse approach is favored by some, especially when performing the procedure solo because it appears to be technically easier to cannulate the vein with this method. It is therefore particularly useful when injecting smaller veins less than 3 mm in diameter. The advantages of the longitudinal approach are, first, that the direction of flow of the sclerosant can be observed and, second, the linear array probes can be used to compress the segment of vein for a length of about 50 mm during the injection, thereby allowing better contact of the sclerosant with the vein wall at the injection site.

The imaging frequency of the transducer used may vary from 7.5 MHz to 15 MHz; the lower frequencies are used for deeper placed subcutaneous veins (>3 cm below the skin) and higher frequencies for more superficial veins. Commonly a 10 MHz transducer is used for its ability to imagine most subcutaneous veins adequately. Most transducers will have an indicator line or LED that will indicate the alignment of the sagittal plane of the transducer. For either approach, the needle is inserted close to the transducer tip and along the sagittal plane of the transducer (see Figure 20.1).[3] When the needle pierces the skin, the tip should be visualized by the ultrasound. Adequate amounts of ultrasound gel need to be applied to the skin to obtain optimum visualization.

As the needle is slowly inserted it appears as a reflective straight line angling toward the target vein (see Figure 20.2). It is important to verify early in the procedure that the needle is being introduced in the correct sagittal plane of the transducer. When injecting in the transverse section of the vein, the transducer can be moved in small increments to align with the needle. When injecting in the longitudinal section of the vein, the direction of needle may need to be altered in small increments, to align with the sagittal plane of the transducer. For either method, the needle and vein should be imaged simultaneously at all times.

As the needle tip makes contact with the target vein, an indentation will be seen on the vein wall (see Figure 20.3). At this stage a little extra pressure is required to pierce the vein wall and after this occurs, the needle can be seen within the lumen and a small amount of blood is drawn into the needle hub to confirm correct intraluminal positioning of the needle tip. A small volume (approx. 0.2 ml) of sclerosant is then injected and should be seen on the ultrasound image to be flowing into the vein (see Figure 20.4). Extravasation is readily visible on the B-mode image and is manifested as a separation between the vein wall and the peri-venous tissues. Should this occur, injection is stopped immediately, and the needle tip is repositioned correctly, or alternatively, the needle withdrawn and reinserted at an appropriate nearby site. When the initial small volume is seen to flow intraluminally, the remainder of the injection is then completed under continuous ultrasound imaging.

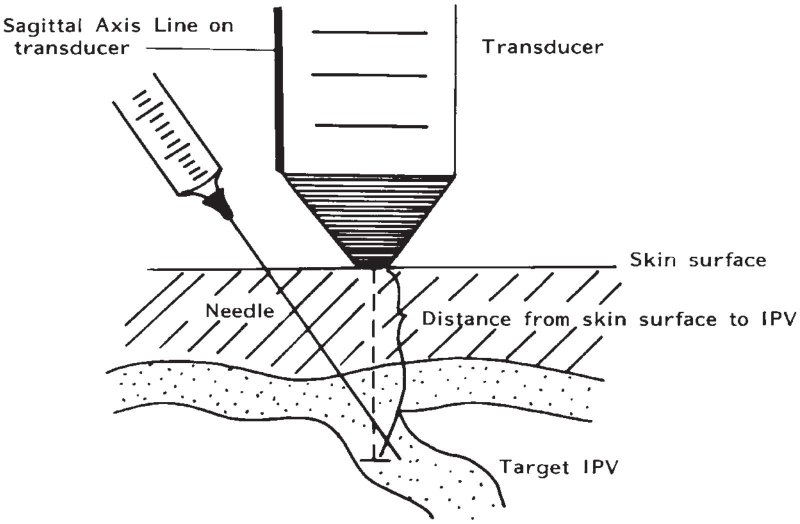

FIGURE 20.1 Correct alignment of the needle along the sagittal plain of the transducer. IPV (incompetent perforating vein). (From Thibault PK, Lewis WA. J Dermatol Surg Oncol. 1992. 18: 895–900.)

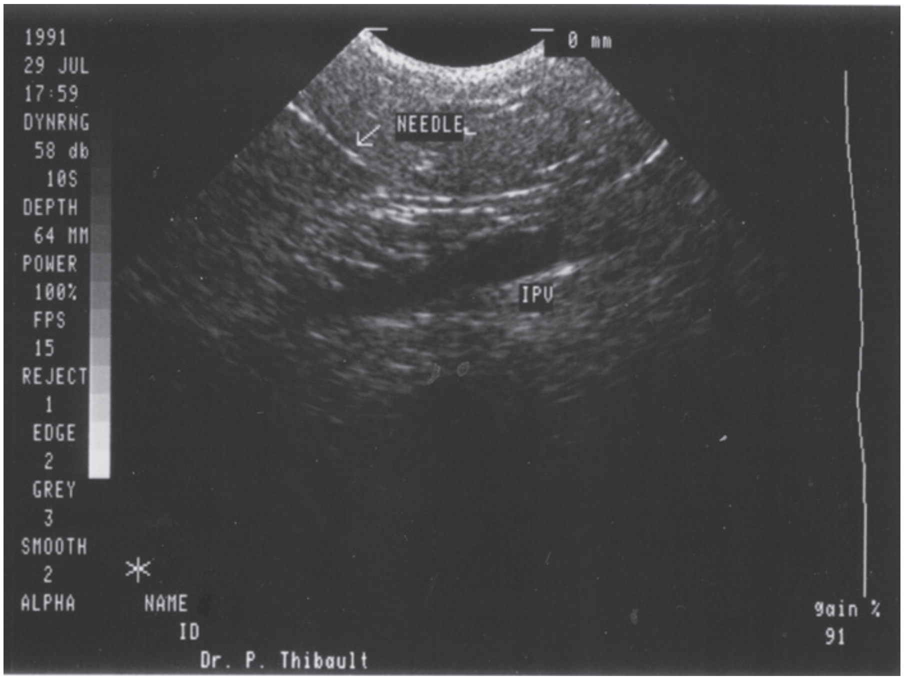

FIGURE 20.2 B-mode ultrasound image of needle angling toward target vein (IPV). The angle of insertion is determined by measuring the depth of proposed injection site on the ultrasound image prior to needle insertion. (From Thibault PK, Lewis WA. J Dermatol Surg Oncol. 1992. 18: 895–900.)

When using the longitudinal approach, during injection the direction of flow of sclerosant can be determined, and with a combination probe pressure and digital pressure applied distal or proximal to the injection site, the direction of sclerosant flow can be modified to optimize the localization of the sclerosant.

The volume of sclerosant injected at any one site varies between practitioners, but usually ranges from 0.25 ml to 2.0 ml depending on the site and size of the vein. It is the author's preference to inject smaller quantities at multiple sites rather than larger volumes at one site, as the former technique, although equalizing the sclerosant concentration

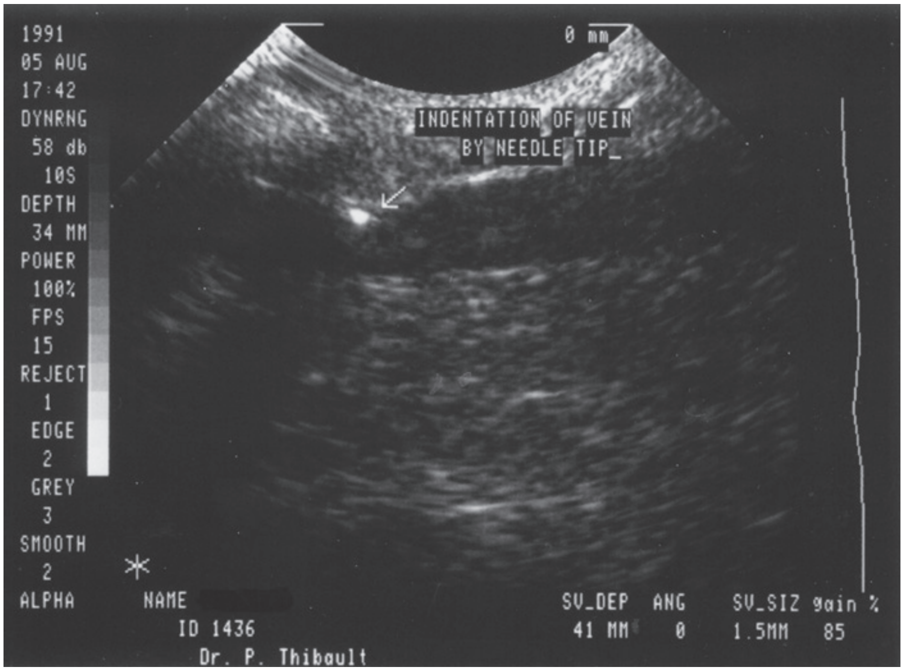

FIGURE 20.3 B-mode ultrasound image of reflective needle tip indenting vein wall immediately prior to vein puncture. (From Thibault PK, Lewis WA. J Dermatol Surg Oncol. 1992. 18: 895–900.)

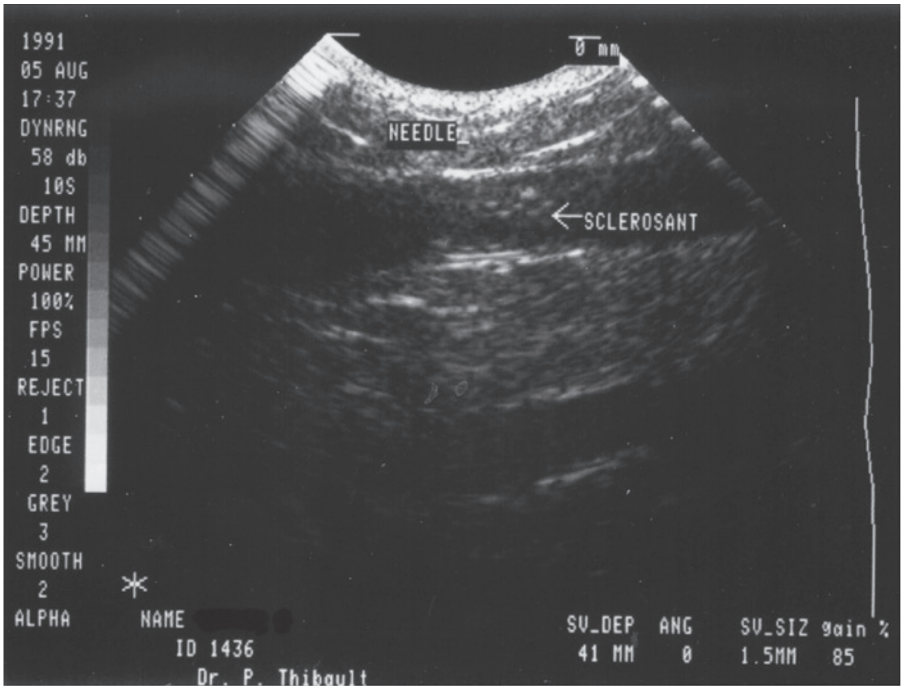

FIGURE 20.4 B-mode ultrasound image of needle located in vein with sclerosant flowing toward the right of image. (From Thibault PK, Lewis WA. J Dermatol Surg Oncol. 1992. 18: 895–900.)

along the segment of vein,[12] minimizes the risk of overflow of sclerosant into the deep system through nearby perforating veins that can cause deep and muscular vein sclerosis and possible subsequent DVT.

When injecting the incompetent GSV or SSV, it is usual to place the first injection 5–10 cm distal to the incompetent saphenofemoral (SFJ) or saphenopopliteal (SPJ) junction. The author uses STS 3% or POL 3% microfoam at a sclerosant: air ratio of 1 : 3. As the recommended maximum dose of Fibrovein™ is 4 ml, the maximum microfoam volume is 16 ml. The maximum volume of POL will vary according to concentration used and patient weight (2 mg/kg/day). When using foam the author prefers to draw up 1.5 ml of foam in each syringe (so this becomes the maximum injectate volume), although many practitioners inject 2 ml at most sites.[6]

Kanter[13] compared the effect of 1 ml and 2 ml sclerosant (3% STS) injectate volumes on immediate vasospasm and later clinical outcomes after UGS. He found that 2 ml injectate volumes were less effective than 1 ml and did not reduce the number of injections given. Therefore this group received twice the volume of sclerosant, and some reported transient flu-like symptoms four to six hours after treatment. Hence, when injecting solution (rather than foam), it is advisable not to inject more than 1 ml at any one site. When injecting within several centimeters of visible calf perforating veins, it is advisable to inject less than 0.5 ml.[3,14]

Injections proceed distally as previously injected segments are observed to spasm or fill with foam. Treatment endpoint is when all segments of incompetent vein have undergone spasm and become incompressible to probe maneuvers. The ultrasound transducer also can be used to compress the treated vein in a rhythmical up and down motion, as the vein is followed post injection to observe for uniform vasospasm. The maneuver also has the effect of uniformly distributing the sclerosant longitudinally and circumferentially along the venous endothelium, thereby accelerating the process of vasospasm.

Catheter Techniques

Open Catheter Technique

In the early days of UGS, especially when the procedure was being developed and techniques refined, there were a number of reports of inadvertent intraarterial injections that concerned many phlebologists.[3,14] Catheter techniques of UGS first were introduced to minimize the risk of inadvertent intraarterial injection and the resultant extensive tissue loss that could occur. The first "open catheter" technique was described by Grondin in 1992.[15] This technique recommended a 20 G 44 mm cannula for cannulation of the GSV or SSV 6 to 8 cm distal to the SFJ and SPJ, which were thought to be the sites of maximum risk of inadvertent intraarterial injection. Correct placement of the cannula could be confirmed by aspiration of nonpulsatile venous blood, ultrasound visualization of the cannula tip, and, finally, injection of normal saline into the vein prior to sclerosant injection. After confirmation that the cannula was inserted correctly into the vein, the sclerosant was injected at that site as a bolus in a similar manner to that described earlier in the "closed" technique. The technique could be used to treat the remaining distal trunk by recannulating distal to the initial cannulation point.

Extended Long Line Echosclerotherapy (ELLE)

The ELLE technique was first described by Parsi in 1997[16] and later reported by Min and Navarro.[17] This technique was developed not only to reduce the risk of intraarterial injection, but also to improve the effectiveness of UGS. Its special indication is the treatment of larger diameter incompetent trunks. This was the pioneer technique, which preceded other catheter-based procedures used to treat varicose veins such as endovenous laser ablation. The technique involves catheterization of a target vein under ultrasound guidance and introduction of the sclerosant as the catheter is withdrawn. Parsi and Lim[18] describe the method in detail.

Cannulation

The entry point for cannulation is selected after completion of pretreatment mapping of the superficial truncal incompetence. The ideal entry point is distal calf for SSV and medial knee for GSV. The segment of vein chosen for cannulation should ideally be straight and superficial. A subcutaneous injection of a local anesthetic is given prior to cannulation. The anesthetic should not contain adrenaline to avoid vasoconstriction.

Cannula Selection and Penetration

The depth and luminal diameter of the selected vein is measured to assist in appropriate cannula selection. Usually 16 G to 18 G cannula are used with cannula lengths varying from 4 cm to 7 cm.

The procedure is carried out using aseptic technique. The vein is visualized with B-mode ultrasound in the longitudinal axis and the selected entry point is marked on the skin. A tourniquet can be applied proximal to the selected point of entry to facilitate the cannulation. Once local anesthesia is achieved, the vein is cannulated under ultrasound guidance. The probe should be perpendicular to the skin and perfect alignment of the longitudinal axis of the probe with longitudinal axis of the cannula should be attempted. Successful entry of the cannula into the vein is signaled by spontaneous venous return. Tapping of the vein with the cannula can cause vasospasm and is best avoided. If vasospasm occurs, it is preferable to choose another point of

entry. Technically, cannulation can be the most challenging part of this procedure.

Catheterization

The length of the selected vein is measured to assist in selection of the appropriate catheter (Cavafix MT134, Cavafix Certo 375) (B.Braun Medical Suppliers, Sydney, Australia). The selected catheter is fed through the cannula (catheter through cannula technique) and introduced into the lumen of the vein and advanced toward the junction under ultrasound guidance. Once the catheter is about 2 cm distal to the junction the leg is raised to 30 to 45 degrees to empty the vein and reduce the vessel diameter. It is this maneuver that is readily performed with the ELLE technique, but more difficult with the closed needle technique, that theoretically will result in better contact of the sclerosant with the venous endothelium with larger truncal veins. The sclerosant is then introduced as the catheter is being withdrawn. Both foam and liquid sclerosants can be used. Some practitioners would compress the junction to prevent the entry of the sclerosant into the deep system (Cloutier technique).[19] Parsi and Lim believe that a number of "pulse" injections of approximately 0.8 ml of STS 3% solution is more effective than continuous and gradual infusion of sclerosant. This is consistent with the principles of sclerosant distribution described by Guex.[12]

Special attention is given to T-junctions with tributaries and perforators as the catheter is gradually withdrawn. Extra volume of sclerosant may be required at these escape points to ensure full sclerosis of these openings. Failure to sclerose the escape points may lead to segmental recanalization of the vein.[4] As with the closed needle technique, the endpoints of the treatment include vasospasm, noncompressibility along the entire length of the treated vein, and absence of any blood flow in the vein, all confirmed with ultrasound.

There are several limitations of the ELLE technique. First, it is not useful in treating complex patterns and tortuous postsurgical recurrences. Second, it is technically difficult to treat smaller incompetent veins less than 4 mm in diameter owing to difficulty in cannulating these veins with a relatively large diameter cannula that is required for the procedure. Its advantages include total avoidance of intra-arterial or extravascular injections, reducing the effective diameter of the target vein, minimizing the number of injections and hence less pain and the ability to reach veins located deep in the subcutaneous tissue.

UGS for Resistant Telangiectases and Telangiectatic Matting

Using a high frequency ultrasound imaging transducer, Somjen et al.[20] have shown that 89% of areas of thigh telangiectases have associated incompetent reticular veins identifiable. A large proportion of these were found to be associated with deeper subcutaneous vein reflux or with perforating vein reflux. Some of the incompetent reticular veins were invisible from the surface and these invisible reticular veins can be a cause of treatment failure when using standard techniques of sclerotherapy. Using high frequency duplex ultrasound, Forrestal[22] also has observed incompetent reticular veins associated with resistant telangiectases and telangiectatic matting. Using ultrasound guidance, these "invisible" veins can be injected with STS 0.5–1% or polidocanol 1%.

Post Sclerotherapy Compression Techniques

External Compression

Various forms of external compression have been recommended following sclerotherapy to varicose veins. Although Fegan advised six weeks of continuous external compression with bandages,[21] this is not generally required with UGS owing to the fact that the principle of the technique is that all proximal sources of reflux are controlled in the initial treatment.

The reasons for using external compression with UGS relate to increased patient comfort, reduction of symptomatic chemical phlebitis and maintenance of optimal deep venous flow during the post injection period. For this reason, the most commonly used compression following treatment is the application of Class II (25–35-mmHg) graduated compression stockings. Generally the stockings are worn during the day for two to three weeks. Some practitioners also advise their patients to wear the stockings at night for the first three to four days in order to maintain optimum deep venous flow in the early post-injection period, thereby minimizing the risk of deep venous thrombosis. The stocking may be removed each day for showering, without any undue adverse effects.

Internal Compression (Perivenous Compression)

This novel method has been introduced recently to improve sclerosant contact with the vein wall during the immediate post-sclerotherapy period. The technique was developed from the perivenous local anesthetic technique for endovenous laser ablation. With this method, following completion of injection of the main stem (GSV or SSV) with sclerosant foam, normal saline with 1 : 500,000 adrenaline is injected perivenously in the compartment between the deep and superficial fascia (see Figure 20.5) at three to four locations equally spaced along the axial vein in the thigh (GSV) or calf (SSV). Usually between 10 and 20 ml of normal saline is required, or about 5 ml at each cross-sectional segment. The injection is performed using ultrasound guidance with a cross-sectional approach using a 25 gauge 1½

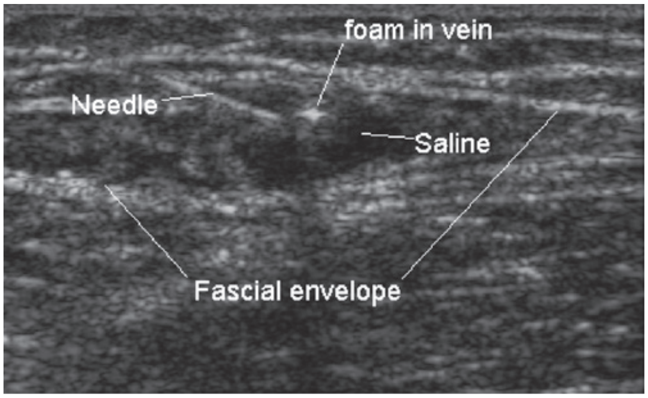

FIGURE 20.5 Post UGS perivenous compression of GSV with normal saline.

inch needle. The effect is to give greater immediate compression to the vein, thereby decreasing the diameter of the already spasmed vessel by approximately another 50%, resulting in better apposition of the veins walls and more complete contact of the veins wall with the sclerosant.

The author now uses this method routinely when treating larger axial vessels (GSV and SSV) greater than 4 mm in diameter and axial veins that have recanalized. Early experience indicates a reduction in early recurrence and recanalization.

Post Treatment Methods and Follow-up

Immediately after treatment, patients are advised to walk continuously for 15 to 20 minutes and are then instructed to walk for at least 45 minutes daily. This significantly improves any discomfort, which is generally minimal. Pain requiring treatment following the procedure is unusual and indicates that the patient needs to be reviewed by the phlebologist to ascertain the cause. Walking reduces superficial ambulatory pressures and ensures high flow in the deep venous system of the leg for a prolonged period at least once per day.

Patients are usually reviewed one to two weeks following treatment, at which time the venous system is reexamined with duplex ultrasound to determine:

1. Whether the treated veins are incompressible and have no flow.
2. The patency and flow in the deep veins.

If a treated segment of vein is found to be partially or completely patent and have persistent reflux, the segment is reinjected using ultrasound guidance. The phlebologist should be aware that lower concentrations of sclerosant might be necessary, as the vein endothelium will be partially destroyed, making the vein more prone to chemical thrombophlebitis if too strong a concentration is used.

At the first post-UGS visit, once proximal closure of the treated veins has been confirmed, residual distal branch varicose veins and telangiectases may be treated with standard sclerotherapy methods. The patient is then reviewed four to six weeks after the initial treatment, when repeat ultrasound examination is performed and any intravascular coagula are removed through a small stab-incision using either an 18–21-gauge needle or no. 11 blade. Generally this procedure can be performed without any anesthesia.

Further follow-up visits may be scheduled at three, six, and 12 months to ensure that there has not been recanalization of the treated vein.

Adverse Effects of Ultrasound-Guided Sclerotherapy

Varcoe[8] performed a survey of 44 experienced UGS phlebologists from seven countries and reported on their experience with adverse effects from UGS. In this survey, side effects were grouped into minor or major reactions. Minor reactions were phlebitis, pigmentation, edema, pain, minor (asymptomatic) DVT, and minor allergic reaction. Major reactions were major DVT, pulmonary embolus, and severe allergic reaction. In this survey, the incidence of major adverse effects was less than 0.1%. Only one phlebologist reported pulmonary embolus occurring, indicating the low risk of this event. In 15 years of performing UGS, the author has not observed any pulmonary emboli following UGS and only one DVT (affecting the popliteal vein extending from a sclerosed gastrocnemius perforating vein).

Several intraarterial injections were reported early on in the history of UGS, [3,14] and the incidence reported in the Varcoe survey was 0.01%. The risk of this event appears to be directly related to the experience and training of the phlebologist in this procedure and rarely occurs in skilled hands.

The most common serious adverse effect experienced by the author has been anaphylactoid reactions to the sclerosant STS.[23] The incidence of anaphylactoid reaction in 2686 treatment sessions was 0.15%. This reaction appears to be concentration and volume dependent. Interestingly, since the advent of foam this incidence has been greatly reduced. The author has not observed any anaphylactoid reactions to STS 3% foam in the past five years.

A relatively common, but minor adverse effect reported after UGS (and possibly more frequently when using foam) is transient visual disturbance sometimes associated with migraine headache and less frequently associated with chest tightness. The mechanism for this adverse effect is not entirely understood and although it has been suggested that it is caused by air passing through a right to left shunt in the heart, the author has never been able to document such a defect in affected patients, and the adverse effect also occurs

in sclerotherapy when foam is not used. The author believes that this is a reflex vasospastic event as the patients affected generally have a past history of migraine.[23]

Short- and Long-Term Results

There are now a number of studies documenting the effectiveness of UGS. Most of these studies have examined the results of treating GSV incompetence although there are several now published on SSV incompetence.

Greater Saphenous Vein Incompetence

The first reported objective ultrasound results of SFJ and GSV incompetence treated with UGS were those of Kanter and Thibault.[4] Using STS 3% solution, they reported a 76% success rate at 24 months. Cabrera et al.[5] followed up 500 lower limbs with SFJ and GSV incompetence treated with UGS using Lauromacrogol 400 (polidocanol) microfoam. After three years, 81% of treated GSVs were obliterated and 96.5% of superficial branches disappeared. The obliteration of saphenous veins required one treatment in 86%, two in 10.5%, and three in 3.5%.

Cavezzi and Frullini[24] in a study of 106 saphenous axes or recurrent postsurgical varices achieved 95% sclerosis at 21 weeks using STS 1% or 3% sclerosant foam. There were three completely unsuccessful cases despite three treatment sessions, and 10 cases of early recanalization (with reflux or retrograde flow), subsequently successfully retreated with UGS.

Myers et al.[25] reported objective ultrasound results on 100 limbs (78 GSV and 22 SSV) after 12 months using STS or Aethoxysclerol™ according to preference and partly determined by the diameter of the veins. All but one vein treated was less than 10 mm in diameter. Echosclerotherapy was successful in the first treatment in 86 limbs (primary success), but it was necessary to repeat treatment once in 11 and twice in three limbs to give the secondary success. At one year, the cumulative primary success was 77% and the secondary success rate was 88%. During the same period, 31 limbs (24 GSV and 7 SSV) were treated surgically (primary treatment) and then with UGS for early recurrence to give a secondary success rate. In this group at 12 months cumulative primary success was 71% and the secondary success rate was 87%.

Several studies have examined the effect that various clinical determinants had on UGS outcomes. Kanter[26] looked at the effects of age, gender, and vein size. He found that larger doses of STS were required to induce vasospasm in older patients, males, and those with larger veins. Regardless of gender and age, larger veins were more likely to recanalize, but were not necessarily associated with clinical recurrence. Although older patients and males tended to have larger veins, their recanalization rates were similar to younger patients and females when sufficiently higher STS doses were used to induce vasospasm. Barrett et al.[27] in a study of 115 saphenous veins treated with STS microfoam UGS confirmed a small increase in failure to close the SFJ and SPJ with increasing size of junction diameter (>10 mm), but this did not significantly alter the results with respect to clearance of visible varicosities and patient satisfaction with results.

In a separate study, Barrett et al.[28] followed 100 randomly chosen legs with varicose veins treated by UGS using STS 3% microfoam after an average of 22.5 months (range 20–26 months). An average number of 2.1 treatments were required to close incompetent varicose veins. Thirty-one percent of legs required a second treatment at the three-month follow-up. Such treatments were generally for a small channel in the saphenous trunk, a small feeding vessel or perforator creating the channel, or minor residual varicosities. Success was analyzed from two perspectives: patient satisfaction and clinical and ultrasound assessment. There was an extremely high patient satisfaction with 100% of patients stating that foam UGS had been successful in treating their varicose veins and related symptoms. Clinically, 92% had complete removal of their varicosities with 5% developing new varicosities related generally to perforator incompetence unrelated to the treated saphenous veins. Duplex examination revealed four saphenous veins with persistent reflux.

Thibault[29] reported the five-year recurrence rate in 35 limbs with GSV incompetence treated with UGS. Nine limbs (25.7%) had recurrent varicose veins clinically. Ten had persistent reflux at the SFJ and 14 limbs (40%) had persistent reflux in the proximal thigh segment of the GSV. Comparing these results with the shorter-term studies indicates that there is a slow but steady increase in cumulative recurrence with time, indicating the need for periodic review and retreatment when clinically indicated in this group of patients.

Small Saphenous Vein Incompetence

Padbury and Benveniste[30] reported patient satisfaction, clinical, and sonographic success in a prospective study on 15 limbs with SSV incompetence. Primary success was achieved in all patients (SSV injected and obliterated). At six months, five (33%) had minor residual varices. Duplex examination at six months revealed one limb with a residual patent incompetent SSV. This patient had a 9 mm vein pretreatment. Patient satisfaction as gauged by the Aberdeen QoL questionnaire demonstrated an excellent response with all patients recording a positive improvement.

Perforator Vein Incompetence

The effectiveness of UGS for incompetent perforator veins (IPVs) was reported by Thibault.[3] Thirty-six patients

(38 limbs) with incompetent perforating veins were treated with UGS using STS 3% solution. The IPVs were classified according to anatomical location as thigh ($n = 12$), gastrocnemius ($n = 13$), or posterior tibial ($n = 18$). Two thigh IPVs, three posterior tibial IPVs, and one gastrocnemius IPV required repeat injection at the six- to eight-week follow-up examination. The IPVs were then reexamined with duplex ultrasound six months after treatment. All (100%) gastrocnemius IPVs remained sclerosed with no flow at six months, 83% of thigh IPVs were sclerosed, and 72% of posterior tibial IPVs remained occluded with no reflux at six months. The difficulty of obtaining good long-term results with posterior tibial IPVs probably relates to the high hydrostatic forces present in the distal leg.

Management of Post-Surgical Recurrent Varicose Veins

UGS has become the preferred management of post-surgical recurrent varicose veins. There are four common sources of reflux associated with recurrence of varicose veins after surgical ligation and stripping: 1) recurrence of reflux at the SFJ or SPJ because of neovascularization or inadequate ligation; 2) incompetent thigh or calf perforating veins; 3) incompetent gastrocnemius veins; 4) persistent varicose tributaries or duplication of the GSV in the thigh, with these medial thigh veins receiving reflux from pelvic tributaries.[31] For obvious technical reasons and to avoid the risks of redo surgery (nerve and lymphatic damage), these sources of recurrent reflux are best treated with UGS.

As with primary varicose veins, there needs to be a thorough mapping of the superficial venous reflux and assessment of the deep venous system in the leg. The segments and points of reflux are then methodically treated using real-time ultrasound guidance. Standard sclerotherapy is then used to treat any residual superficial varicosities one to four weeks later.

Management of Venous Ulcers

Foam UGS has been reported to be an effective method for accelerating healing of venous ulcers associated with superficial venous incompetence.[32] Thirteen patients with lower leg ulceration clinically suggestive of venous ulceration were confirmed to have superficial venous incompetence with or without deep venous insufficiency. The average ulcer duration was 27 months (range 3 to 96 months). The 13 limbs then were treated with foam echosclerotherapy to all areas of superficial venous incompetence detected on duplex scanning. Nine patients had complete healing of their ulcers within five months of commencing treatment, two ulcers healed by 12 months and another healed after 20 months. The remaining patient's ulceration was still improving but not fully healed at 14 months.

The advantage of this approach is that the underlying cause of the ulceration is addressed, thereby reducing prolonged morbidity and cost of long-term management of chronic venous ulceration.

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CHAPTER

21

Sclerofoam for Treatment of Varicose Veins

JEAN-JÉRÔME GUEX

HISTORY AND BACKGROUND

Sclerofoam is not a brand new idea. Many authors have presented their own recipes, and sometimes results, decades ago.[1] However, Sclerofoam became much more popular after Cabrera's (in Spain) and Monfreux's (in France) first presentations.[2,3] After a period of reluctant observation by mostly surgeons unaccustomed to sclerotherapy foam, they began to raise unexpected interest since it "worked amazingly well"!

At that time, "evidence-based medicine" had expanded its influence over the world, and had even penetrated phlebology. The time had come for a true evaluation. The problem was the usual one in trying to apply the rules of evidence-based medicine: Sclerofoam worked so well that nobody wanted to waste time to demonstrate what was obvious.

The final (salutary) pitfall to test foam sclerotherapy was the demonstration of efficacy presented by endovenous ablation, VNUS Closure©, and Laser EVLT. The subsequent combination of methods frustrated any attempt to test each new technique. Despite this problem, thanks to several authors we now have evidence on which to base our medicine. A little more "medicine-based evidence" is still necessary.[4]

With all the new techniques, the problem has been that during the last 10 years treatments have evolved faster than the varicose veins of patients. The time tested and multiply requested long-term evaluations were not feasible in the short period of time after introduction of each new technique. It became obvious that new ideas sprouted before outcomes of the previous ones were harvested.

WHAT IS SCLEROFOAM?

Advantages and How to Prepare It

All details of all the techniques are extensively and sufficiently described in the literature.[1] So we will focus on the most commonly used and well-described methods.

Sclerofoam is obtained by mixing a liquid with a gas. For sclerotherapy, detergent sclerosing agents such as Polidocanol (POL) and Sodium Tetradecyl Sulfate (STD or STS) are the most logical ingredients. The usual gas is air, although many others have been tried or are being used. Foam is obtained after repeated alternate passages from one syringe to another through a connector that may have a reduced diameter to decrease the size of each foam bubble. This has even been automated in order to standardize foam (Turbofoam®, I2M, Caen, France). Foam will vary according to the nature of the sclerosing agent: POL or STS and in its initial concentration; according to the nature of the gas and to the ratio (volume of liquid/volume of gas) of the mixture. This and the preparation mode can modify the size of bubbles, their range of diameters, the "wetness" of the foam, and its overall stability. These characteristics probably change the power and efficacy, but there are so many variables that this is unclear so far.

Compared to liquid sclerosing injections, foam has several advantages: a smaller quantity of sclerosing agent to inject, no dilution with blood, and it ensures an even and homogenous effect along the injected vein, provided the diameter remains reasonable (see Figure 21.1).[5–7]

Another advantage of foam is its ultrasound echogenicity. Liquid/air interfaces act like reflectors and foam appears as

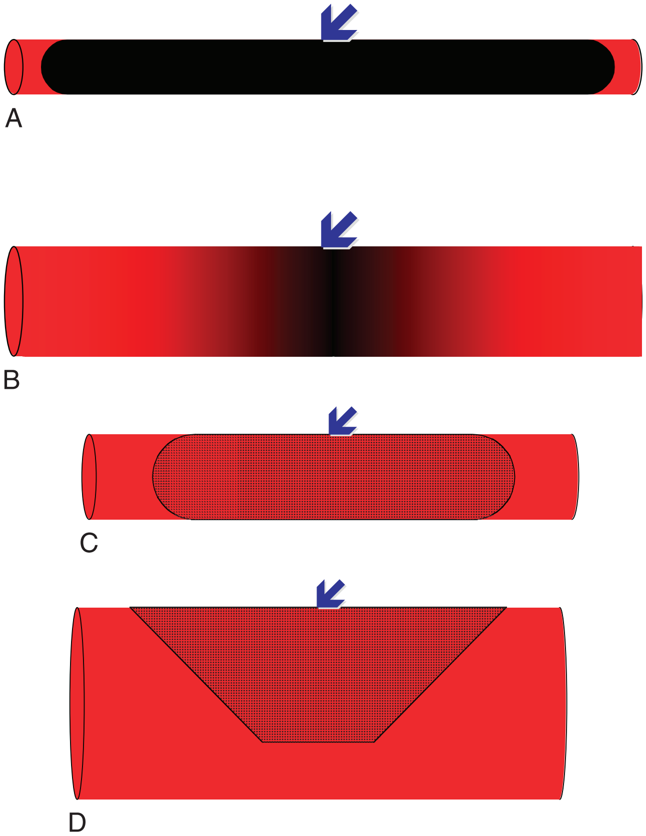

FIGURE 21.1 **A**: In small veins (<3 mm), liquid sclerosants do not mix and replace blood. **B**: In medium sized (4<ø<12 mm) varicose veins, liquids dilute with blood, efficacy is satisfactory only near the injection site. **C**: Injection of foam fills-up the vein so that its efficacy is homogenous. **D**: In large veins, foam floats so its action is limited to the superficial wall, thus the importance of obtaining venous spasm.

Except in small veins (**A**), liquid sclerosants are diluted by blood and their efficacy is correct only near the injection site (**B**), where the concentration is powerful enough to initiate a sclerosing reaction.

The main advantage of foam is that it does not mix with blood. It displaces blood and replaces it in the vein lumen (**C**). The concentration of active sclerosing agent along the wall is then perfectly homogenous and even. This ensures an excellent result except when the vein is too large and due to its low density, foam floats in contact with only the more superficial wall (**D**). Obtaining a reduction of venous diameter by any means, especially by venous spasm, is therefore of utmost importance. (Goldman MP, Bergan JJ, Guex JJ. Sclerotherapy, treatment of varicose and telangiectatic leg veins, 4e. New York: Elsevier. In press.)

an excellent contrast medium, even when only a few bubbles are present. At that stage it has the appearance of a cloud. More dense, foam is completely opaque to ultrasound and is completely white, with an underlying acoustic shadow. This characteristic is helpful in following foam when injected from a remote injection point.

As derived from Tessari's method,[8] the most common method of making foam uses two 5 ml Luer-lock siliconized syringes. One syringe contains 1 ml of sclerosing agent at the desired concentration, the other 4 ml of (sterile, filtered) room air. Syringes are connected either by a three-way stopcock or a female/female luer-lock two-way connector. Then foam is obtained by cavitation by an average of 20 back and forth passages from one syringe to the other. Stability of this kind of foam is correct for one to two minutes, no more.

A type of commercial foam was still undergoing clinical trials at the time of preparation of this chapter, Varisolve®, based on Cabrera's initial microfoam but transformed to allow a canister-contained mixture to produce ready-made foam. This system is designed to provide standardized Polidocanol foam that is FDA approved. Although practical interest in this foam is intense because of its proposed sanction, this is tempered by its cost. Its superiority to homemade foam remains to be demonstrated.

INJECTING SCLEROFOAM

Two groups of different methods are used to inject sclerofoam. Authors usually favor one but use several, if not all, in various situations. Sclerofoam is mostly used for large veins, thus it is usually injected with duplex guidance and duplex control of efficacy.

One main difference is in the method of venous access, which can be either an open vein access (butterfly needle, micro-catheter, long catheter) or a direct puncture of the vein with the needle mounted on the syringe. Open-vein access provides optimal safety since it uses devices designed for safe and durable venous infusion and allows easy continuous control of blood reflux and adequate positioning of the needle (see Box 21.1).

Open-vein access allows injection of any volume and repeat injections with additional syringes if necessary. It is important to emphasize the fact that open-vein access allows preparation of the foam at the last minute, and rapid injection of fresh foam. Short catheters and butterfly needles have almost the same utility.

Long catheters are still uncommon but will open a new perspective. The tip can be placed at any level, for example the (SFJ) junction. After positioning, the leg can be elevated and an Esmarch bandage applied. This empties the vein and then the foam is injected while pulling back the catheter. This technique, in principle, is comparable to endovenous ablation, but is much cheaper. Preliminary results are encouraging but the technique is more complicated than open-vein access. Its advantages remain to be demonstrated.

VARICOSE PATTERNS WHEN CONSIDERING A SCLEROSING FOAM TREATMENT

Sclerofoam allows filling of a quite long segment of vein from a remote puncture site. Therefore, duplex scan evaluation of varicose patterns must take into account preferential

BOX 21.1

Step by step ultrasound-guided. Sclerofoam injection with open venous access. This assumes that a preliminary duplex assessment and mapping of all veins of the lower extremities has already been carried out and that results have been carefully reviewed.

- Prepare all necessary materials on a tray:
  - 25G × 3/4″ butterfly needle (for veins no deeper than 1 cm) or needle with connector
  - 2 × 5 mL luer lock needles, one containing 1 mL sclerosing solution, the other 4 ml of sterile air, attached by a three-way stopcock or two-way connector
  - Adhesive tape, elasto-adhesive tape, cotton balls, medical compression stockings
  - Sterile US gel, sterile probe cover
- Map the area to treat with duplex (10 MHz probe necessary), draw the network to treat, including possible points of injection
- Prepare skin
- Place needle into varicose vein under US guidance with bevel turned down
- Check reflux of blood in hose or connector; attach to skin with adhesive tape
- Prepare Sclerofoam by 20 alternate passages from one syringe to the other
- Attach syringe to connector
- Place probe over needle, check position
- Inject first bubbles; check on duplex that bubbles are inside the vein
- Inject Sclerofoam, control filling of varicose network with duplex; if necessary massage with probe or hand to fill the desired venous network
- Check appearance of venous spasm
- Remove needle, apply cotton ball and adhesive tape
- Place foam pad (option), elasto-adhesive tape, and finally grade 2 medical stockings
- Take some time while the patient is still on the table to explain that walking is recommended, that stockings must be kept on for 24 hours, and then for two weeks daytime only
- Make appointment for next session (duplex evaluation and other injection if necessary).

channels and not just the raw mapping of eye-visible and echo-visible veins. For instance, the association of incompetent varicose medial leg and thigh tributaries joining an incompetent saphenous vein at mid thigh should be emphasized in the scan report. This is one of the best primary indications for foam sclerotherapy. This pattern requires proper assessment of diameters of both the tributary varicosity and the saphenous trunk. Many physicians consider that sclerosing the tributary is the primary aim of their injections. Others adhere to old surgical dogma that the refluxing saphenous vein must be obliterated (first or at the same time).

Current respect for the dogma of systematic elimination of reflux at the SF junction may disappear after several years of use of endovenous ablation that preserves the junction. The next, possibly successful, heresy could be to reject saphenous trunk treatment entirely in some cases.[9]

ADVANTAGES OF SCLEROFOAM

Comparison with Other Sclerosants and with Other Methods (Surgical, Endovenous Ablation)

Choosing Sclerofoam treatment for large veins is an option. But it implies certain prerequisites and corollaries such as:

- Expertise of the treating physician
- A clear understanding and agreement between patient and physician on a treatment program requiring several sessions, additional, repeat injections, and control scans
- Important benefits such as ambulatory procedures without even local anesthesia but with optimal cosmetic results and cost effectiveness

Even today, short and mid-term results[10–13] of foam sclerotherapy are not inferior to surgery or endovenous ablation. But long-term results are still under evaluation. Since repeat injections are simple, cheap, and cause no disability, evaluation of outcomes of Sclerofoam treatment should not require the same endpoints as surgery.[14]

Sclerofoam sclerotherapy has progressed thanks to a better understanding of pathophysiology of varicose disease caused by duplex ultrasound experience. For a long time, some 100 years, junctional reflux has been considered as the main, if not the only, problem. All treatments up to 1990 were devoted to its eradication. More recent conceptions, however, take into account the role of the varicose reservoir. This is a necessary drainage for incompetent trunks. It allows demonstration of actual reflux. The varicose reservoir addresses different perforating veins differently. These are very often not only nonpathogenic but also a necessity to drain varicose clusters (reentry perforators). This understanding of the reservoir function of refluxing varicosities is also applicable to surgical approaches. A common observation is that treating large refluxing tributaries and varicose clusters can reduce or totally suppress truncal reflux. How to decide in which cases such an approach is optimal is still undecided.

HOW MUCH TO INJECT?

The main advantage of Sclerofoam is that it fills up the varicose vein without being diluted with blood. It is important to adjust the injected volume to the length and diameter of the vein. This can be estimated by a simple calculation using the formula of the cylinder: $V = \pi \cdot (D/2)^2 \cdot L$ (V = volume, D = diameter, L = Length).

Several results are presented in Table 21.1.

TABLE 21.1 Volume in cm^3 of a Venous Segment Calculated from the Formula of the Cylinder (from Reference 5)

Vein diameter in cm	Vein Length in cm							
	5	7	10	15	20	25	30	35
1.00	3.93	5.50	7.85	11.78	15.71	19.63	23.56	27.49
0.90	3.18	4.45	6.36	9.54	12.72	15.90	19.09	22.27
0.80	2.51	3.52	5.03	7.54	10.05	12.57	15.08	17.59
0.70	1.92	2.69	3.85	5.77	7.70	9.62	11.55	13.47
0.60	1.41	1.98	2.83	4.24	5.65	7.07	8.48	9.90
0.50	0.98	1.37	1.96	2.95	3.93	4.91	5.89	6.87
0.40	0.63	0.88	1.26	1.88	2.51	3.14	3.77	4.40
0.30	0.35	0.49	0.71	1.06	1.41	1.77	2.12	2.47
0.20	0.16	0.22	0.31	0.47	0.63	0.79	0.94	1.10

TABLE 21.2 Concentrations and Volumes for Polidocanol® Foam (from Reference 5)

Vein	First session (%)	Second session (%)	Volume (cm^3)
Thigh GSV	1.5	3	Up to 8
GSV main tributary	0.5	1	Up to 4
SSV	1.5	3	Up to 4
Perforators	1	2	Up to 2
Nonsaphenous site	0.5	1	2 per

Nevertheless, it must be remembered that venous spasm will occur after injection and that massage or alternate compression and release are thought to increase spasm. The actual volume necessary for an appropriate result is probably less than that listed in the table. Duplex control of the distribution of the foam is essential and allows adapting the volume to specific conditions. From this point of view, open-vein access makes the procedure easier since it allows waiting and seeing and reinjecting if necessary.

We have recommended limiting the volume of Sclerofoam as in Table 21.2. This is also recommended by the European consensus.[15]

SIDE EFFECTS OF SCLEROFOAM

Sclerofoam sclerotherapy shares most of its (rare) side effects with usual sclerotherapy but some complications are more specific. Visual disturbances are frequently quoted as one of the main inconveniences of foam, but there is evidence[16] that they are more related to big bubbles than to microbubbles. When visual troubles were observed with liquid, it was mainly associated with the use of the air block technique. After sessions using only Sclerofoam, we observed less than 0.25 visual adverse effects per 100 sessions.

Foam is an excellent contrast medium for ultrasound. Therefore duplex-guided sclerotherapy with foam dramatically improves the safety of sclerotherapy injections with regard to intraarterial or extravenous injections. We observed no case of necrosis in the French registry[16] and the number of such accidents by French Malpractice Insurance Company has decreased to zero these last two years.

Venous thrombosis is a complication that has been considered as one of the main drawbacks of sclerotherapy. In fact, deep venous thrombosis has been observed in very few cases: one DVT in more than 6000 sessions.[16] Other thrombotic complications also have been observed in other venous compartments: extension to perforating veins (two cases) and to muscular veins (three cases). Appropriate treatment by compression and low molecular weight heparin or nonsteroidal anti-inflammatory medications has always been successful. No pulmonary emboli have been observed in this series of over 6000 cases. Thrombophilia is suspected in these cases but is not the only etiologic factor.

Another side effect that must be emphasized is the increased sclerosing power and the possible excessive inflammatory or phlebitic reaction produced by the foam. More than a complication, this is a manifestation of efficacy of the technique; it indicates that some serious knowledge and practice are prerequisites to its use!

After injection, some hardening of the tissues and tenderness commonly is observed, even with appropriate compression. The content of the vein is variable and unclear, sometimes made of pure blood elements, sometimes containing fibroblasts. Frequently, around the sixth week, the vein fills again with blood; this might be related to destruction of the most central layers of the venous wall and bleeding of the vasa vasorum. This inconvenience is easily cured by small thrombectomies carried out with a large needle or trocar.

The potential risk of allergy has always been mentioned in papers devoted to sclerotherapy. However, we did not observe a single case in the French registry. It makes sense to consider that foaming does not increase the risk. However, several (probably less than five) cases of lethal anaphylaxis

have been reported with liquid sclerosants, and such an event must be explained to patients in the consent.

The question raised by detection of bubbles in the left heart circulation is still unanswered but several factors seem clear: passage through a patent foramen ovale is possible in certain patients. No clinical detection is possible, no pre-treatment detection is required. Isolated bubbles, meaning there is no cluster of microbubbles, because in the injected area they are made only of gas; the interface with blood does not carry a significant number of sclerosing agent molecules, because they have been diluted. The question of possible pulmonary sclerosis induced by bubbles is still theoretical and has not been observed clinically.

SCLEROFOAM WITH AND WITHOUT U.S. GUIDANCE

Obviously, very superficial veins do not need ultrasound guidance for access and foam can be injected after puncture and simple observation of blood reflux. Furthermore, very superficial veins are seen only with specific high frequency probes that are not always available. Anyway, controlling the passage of the foam into upper, bigger, and deeper veins is always useful. It is also necessary to remember that in veins smaller than 3 mm, foam has no advantage over liquid. Appropriate preliminary venous mapping is required in all cases of varicose vein treatment; post-treatment; ultrasound assessment of results after several days or weeks is also common practice for most phlebologists.

SCLEROFOAM FOR TRUNCAL VARICOSITIES

Truncal varicosities must be assessed carefully by duplex for their whole length. This is true especially for the Great Saphenous vein, because valvular incompetence is not necessarily total and very often the terminal or preterminal valves are competent. In this situation, this part of the vein will not need to be treated. It is also necessary to remember that the saphenous trunks are always intrafascial. The frequent confusion between a varicose medial superficial tributary and the GSV trunk is responsible for some inappropriate management of varicose vein patients. What must be done and what is appropriate is different in a saphenous trunk with its thick venous wall and distensibility limited by its intrafascial position and in a tributary, even of large diameter with its thin venous wall, remodeling, sensitivity to sclerosing agent, and slow blood flow.

The approach to complete GSV incompetence, including the saphenofemoral junction, can be accomplished by direct puncture in the upper third of the thigh and injection of a limited amount of concentrated Sclerofoam with a trend toward reduction of concentration and an increase in volume and successive injection of the distal trunk. Nobody advocates injection at the junction level anymore. Our preference is for a more distal approach, at lower third of thigh, with open-vein access and filling of the whole vein. This approach ensures safety and comfort for patient and physician. Difference of efficacy between the two methods is unknown so far.

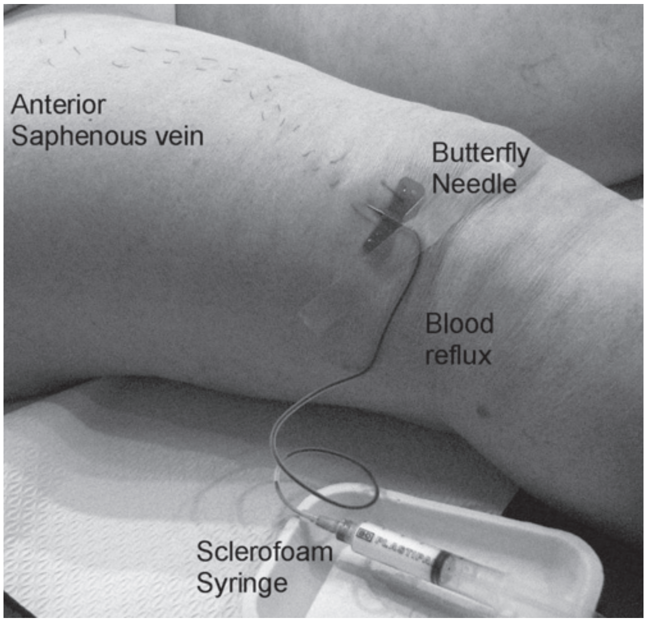

FIGURE 21.2 This photograph shows the butterfly needle taped in place, the foam in the syringe ready for injection and the target vein marked for reference purposes.

Due to the depth of saphenous trunks and their relative autocompression by saphenous fascia, thrombectomy after foam sclerotherapy is usually not necessary.

SCLEROFOAM FOR TRIBUTARIES

Sclerofoam power allows treatment of a vein with a mild concentration of sclerosant, which ensures a homogenous and even reaction. Tributaries are usually more superficial than trunks and their access is easy with butterfly needles (see Figure 21.2). If carefully used, with a lower concentration, Sclerofoam decreases the incidence of matting and residual pigmentation. As explained earlier, thrombectomies may be necessary at four to seven weeks.

SCLEROFOAM FOR PERFORATORS

Perforating veins again raise a common problem: Must we get rid of all visible or identified dilated veins? Specifically, is duplex observation of reflux in a perforating vein sufficient to decide that this vein must be treated (sclerosed,

ablated, and ligated)? This is not certain,[17,18] and in many cases, perforating veins act as drainage of varicose clusters (reentries) and their size decreases significantly after appropriate treatment of the varicose network situated proximally. This is especially true for Cockett perforators (lower third medial lower leg), and much less likely for perforating veins of the femoral canal (medial thigh). More precise assessment criteria are needed in order to limit treatment to what is necessary, but a first approach is to begin the treatment with the upper network (probable source of reflux) and to finish with lower elements including perforators (possible reentries).

If Sclerofoam treatment of perforating veins is carried out as in other veins, special attention must be paid to avoid progression of foam into the deep network. For this reason, duplex control of foam distribution is essential.

SCLEROFOAM FOR C4-C6 PATIENTS

In case of chronic venous insufficiency, Sclerofoam has demonstrated excellent results,[19] and provides dramatic improvement in skin changes A peri-ulcerous injection of Sclerofoam appears to be a booster to wound healing.

SCLEROFOAM FOR RECURRENCES

REVAS (REcurrent Varices After Surgery) have been the subject of an international consensus conference.[20] At the time of conference, classical sclerotherapy with liquid was presented as the method of choice for management of such cases. However, the use of foam is even more efficient and more practical.

At the SF junction, two mechanisms have been identified: neovascularization, where small veins appear in hard scar tissue and the lymph nodes; and a persistent saphenous stump, corresponding to an inappropriate ligation and division. In the first case, direct injection with duplex guidance is possible but requires skill. A remote injection with open-vein access allows extensive filling of the recurrent network. In the second situation the objective is close to a primary treatment. Sclerofoam is the treatment of choice. Recurrent varices have unusually thin walls and are prone to easy sclerosing. There is no need for strong concentrations; 1% or less POL is usually enough.

SCLEROFOAM FOR RETICULAR AND SPIDER VEINS

Since most visual complications are observed after use of Sclerofoam and since superiority of Sclerofoam is counterbalanced by an increase of matting and pigmentation related to an increased sclerosing power, we reserve the use of Sclerofoam for telangiectasias and reticular veins to rare, individual cases.

SCLEROFOAM EXCEPT FOR THE LOWER LIMBS

Arms: Varicose veins of upper limbs including fingers are rare; we have treated some with Sclerofoam and observed good results, and it seems unlikely that any large study will be available on this matter. Regarding sclerotherapy of hand veins in elderly patients, we do not recommend any such suppression. Ambulatory phlebectomy has been proposed, and this kind of treatment of "normal" veins is likely to be questioned if a venous access is later necessary for other medical reasons (blood tests, chemotherapy, and emergency IV injections).

Face: Facial veins are small, foam is not needed, and liquid sclerosants are usually efficient. We have observed several good results in sclerotherapy of telangiectasias associated to venous malformations of the face.

CONTRAINDICATIONS OF SCLEROFOAM

As indicated earlier, Sclerofoam is responsible for very few side effects. However, it should be avoided in patients with severe thrombophilias, and carried out with prophylaxis in less severe thrombophilias. There is a prospective study currently in progress in France on this very matter.

Known allergy to POL or STS will not allow the use of the specific agent, but there is no crossed allergy between these agents.

Disulfiram (DCI) is a principal contraindication, but the total amount of alcohol in POL foam is so low that an effect is unlikely.

Tamoxifen (DCI) has demonstrated a potential to induce superficial venous thrombosis during sclerotherapy; therefore, injections must be postponed to the end of chemotherapy.

There is usually no emergency in treating varicose veins, so a Sclerofoam treatment during pregnancy is usually not necessary. Nothing is known about effects of sclerosing molecules on embryos; the principle of precaution should be applied.

PREREQUISITES FOR CARRYING OUT FOAM SCLEROTHERAPY

Physician

- Good understanding and knowledge of venous disorders
- Good practice of duplex on veins

- Previous experience of liquid sclerotherapy
- Skill with syringes and needles
- Time devoted to training for duplex-guided injection on phantoms or beef liver
- Availability for repeat injections

Patient

- Patience
- Understanding of procedures and post-procedure care

CONCLUSIONS

Even if the physician is open to all available techniques, his personal preferences influence his management of varicose disease even before the assessment of varicose patterns. Satisfaction of the patients' main concern should be his motto, and Sclerofoam will appear most of the time as the most "patient-friendly" method. In any case, carrying out such a treatment requires skill and preliminary learning and training.

Progress in Sclerofoam technique is likely to revolutionize the management of varicose disease. We have always advocated an à la carte treatment of varicose veins and it is now obvious that what we did surgically several years ago can be done with Sclerofoam injections. Active, simple, cheap, and safe, ultrasound-guided sclerotherapy with foam is the future of varicose treatments.

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CHAPTER

22

Sclerosants in Microfoam: A New Approach in Angiology

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INTRODUCTION

The onset of reflux and the subsequent development of varicose veins require a connection between the triad made up of the origin of reflux, the transmission route, and the end vessel. These three elements are present in all patients with varicose veins. The first can be identified readily, especially with hand-held Doppler or duplex ultrasound. Then it can be eliminated. It is the least important because isolated absence of functioning valves in any site is of little importance if the blood has no place to go and nowhere to move in retrograde direction. Transmission routes are anatomically highly variable but are readily identified using physical examination and duplex ultrasonography. Their stable elimination can be confirmed by follow-up studies.

The key to therapeutic success in treating venous insufficiency lies in the complete, rigorous, and confirmed elimination of all varicose veins of leg, ankle, and foot. If this objective is not achieved, the incomplete outcome may lead to recurrence. Both endoluminal and surgical procedures, when used alone, face difficulties in completely eliminating all varicose veins in a limb. Even when these approaches are combined some incompetent veins may persist even though they are poorly developed at the time of treatment. These missed veins may be a likely cause of recurrence of varices after varicose vein treatment.

Sclerotherapy, a classic therapy of recognized potential[1] but limited effectiveness, has entered a new era.[2,3] The drastic limitations imposed by its use in liquid form, subject to progressive dilution and inactivation in the blood and very difficult to control when within a vessel, have been overcome. Since 1993, our experiences and that of others have demonstrated the effectiveness of duplex ultrasound-guided microfoam sclerotherapy. This has been used in patients with varicose leg veins traditionally indicated for surgery,[4–6] for venous malformations that resist surgical treatment,[7] and for leg ulcers caused by venous hypertension,[8,9] thus extending the limits of sclerotherapy and raising expectations for this approach.

The old concept of foam sclerotherapy has been brought back to life. A simplistic analogy between foam and microfoam, the great ease with which foam can be produced, and the absence of available pharmaceutical grade microfoam have led to a multiplicity of efforts to use foam for sclerotherapeutic purposes. There have been numerous reports of results obtained with heterogeneous types of foam produced by various but similar homemade methods,[10–14] using even more varied administration techniques. However, major differences in the physics and intravascular dynamics of foams and microfoam, especially the specific pharmaceutical grade microfoam currently under development, suggest that a cautious view should be taken toward the use of foam. At the very least, the recommendations of the Tegernsee consensus[15] should be followed on the injectable volume of homemade foams.

Drawbacks of foams include their use of atmospheric air or even less soluble gases,[16] their high degree of coalescence, and their variability in internal cohesion in the dose of liquid sclerosant that a given volume of foam contains and in the diameter of the bubble.[17]

Microfoam has overcome these shortcomings. Nevertheless, optimization of the application technique and the development of increasingly effective safety measures remain an ongoing challenge.

MECHANISM OF ACTION

Micronization of the bubbles creates an optimal structure to endow the liquid sclerosant with the largest possible surface area and to facilitate its contact with the endothelial surface. The active surface area of the sclerosant liquid exponentially increases with a reduction in the diameter of the bubbles. When these sclerosant vectors possess the appropriate internal cohesion, they can physically displace the blood contained in the vessel. In this way, the liquid can be homogeneously distributed at a known concentration on an extensive endothelial surface.

The diameter of the bubble, the gas-liquid proportion, the internal interbubble cohesion, and the type of gas used are all key parameters, and the efficacy and all-important safety of the procedure depend upon their correct combination. Our patented microfoam successfully incorporates these basic elements and has, in combination with a correct therapeutic technique, yielded previously unmatched therapeutic outcomes with a wide margin of safety.

Although different types of foam can offer more effective treatments compared with liquids, they may not be safer. Homemade foams are distanced from the standards required to consider them a pharmaceutical grade option because of the gases used, the variable dose of liquid sclerosant in a given volume of foam and their even more variable physical characteristics. They represent a stopgap measure before the desired arrival of a registered and standardized product.

FIGURE 22.1 Inflammatory reaction after injection of POL microfoam in a superficial varicose vein.

SAPHENOUS VEIN TREATMENT

In our technique for treating the great saphenous vein, 1% Polidocanol microfoam is injected using a 20G Abbot catheter (51 mm length) placed in the vein at mid/lower third of the thigh in distal direction. With the leg raised, we inject the volume required to totally fill the saphenous in the thigh (filling volume). When the microfoam is seen to arrive at the saphenofemoral junction, the injection is stopped. Approximately 10–20 cc usually is injected, depending on the dimensions of the vein. The microfoam must remain confined to the vein to avoid filling the superficial tributaries at this high concentration, thereby preventing overdose of superficial veins and a resulting inflammatory reaction (see Figure 22.1).

We then aspirate with the syringe to see the color of the intraluminal content, repeating the injection of an appropriate volume (renewal volume) one or two times, if necessary, until a white aspirate is seen, indicating that the segment contains only microfoam. The renewal volume is considerably smaller than the filling volume because the vein segment already contains microfoam, and only 2–3 cc are needed to effectively renew the content. Excess microfoam drains into the femoral vein but is practically inactive, since it is at the proximal end of the "pneumatic piston" that displaced the blood in the vein at the first injection and has undergone major dilution and inactivation.

HEMODYNAMIC FACTORS

Blood is the main adversary of effective contact between a known concentration of sclerosant and the endothelium of large varicose veins. The blood volume can be markedly reduced by elevating the leg, thereby decreasing the pressure and facilitating displacement of the blood by the microfoam, allowing homogeneous contact of the microfoam with the entire endothelial surface (see Figure 22.2). However, leg elevation does not halt the proximal flow and dilution of the sclerosant persists. Proximal flow can be stopped by placing an elastic ligature over the internal condyle. This ligature also avoids passage of the microfoam to varicose leg branches, which are treated at a later session with microfoam at an appropriate concentration.

After the procedure, a 23 mmHg compression stocking is placed and the patient remains resting for 10 to 15 minutes. During this resting period, most injected bubbles, now only deactivated sclerosant-free bubbles of gas, drain into the general circulation. This deactivation of the bubbles is

FIGURE 22.2 Contact of the sclerosant with the endothelium induces a severe vasospasm, a good and immediate marker of the effectiveness of the injection.

produced by fixation of the sclerosant molecules on the enormous surface area of red blood cell and venous endothelium. At the same time, the highly soluble gas is dissolved in the blood, a process that is completed in the lung thanks to its enormous vascular surface area of around 150 m^2.

With foam, it is more critical than with microfoam to accurately determine the length of segment to be treated in order to deliver a volume that precisely matches the volume to be filled. It is not enough to let the foam float on the blood; a specific segment must be filled. As mentioned earlier, we are able to test the filling of a segment with microfoam by reaspiration with the syringe, using the simple method described. If the aspirate is red, there is great dilution and the injection must be repeated. If the aspirate is white, the vessel is completely filled with microfoam and the dose applied to the target tissue is known.

This assessment of intraluminal content by aspiration cannot be used in the treatment of incompetent leg perforating veins when the needle is close to the perforating vein, because the aspirated blood derives from the nearby deep venous system and its filling must not be forced. This type of situation is resolved by precisely matching the volume of injected microfoam to the capacity of the vein to be treated.

Unlike microfoam, homemade foams are limited by the maximum volumes it is recommended to inject. For this reason, sclerosis of an extensive venous area must be performed in smaller stages if foam is used.

FOLLOW-UP CARE

The patient, still wearing the compression stocking, returns to the clinic 10 to 15 days after the treatment, when we confirm the occlusion of the treated proximal segment and check the involution of varicose veins tributary to this segment (see Figure 22.3). At this second treatment session, we adjust the concentration of sclerosant to the location and reduced size of these veins. The appropriate concentrations of Polidocanol are 0.18–0.27%, injected with a 25G butterfly needle; the moderate diameter of the needle limits the flow of microfoam and is consistent with the size of the injected vessels. At this stage, the smaller size of the veins (by involution) allows a larger area to be treated for the same amount of microfoam.

Treatment of small skin veins requires a special approach, using fine needles (30G) and lower concentrations (0.18%). The lesser foaming capacity at these low concentrations and the high mechanical stress suffered by large bubbles when they pass through these fine needles can cause restructuring of the bubbles when foam is used, with most returning to their original components of gas and liquid. This is the usual cause of complications of the foam treatment of small veins and is caused by the injection of atmospheric nitrogen, with its very low solubility in blood. Micronization of the bubbles is especially necessary for sclerosing this size of vein, and for many professionals, the treatment of these small vessels represents the bulk of their practice.

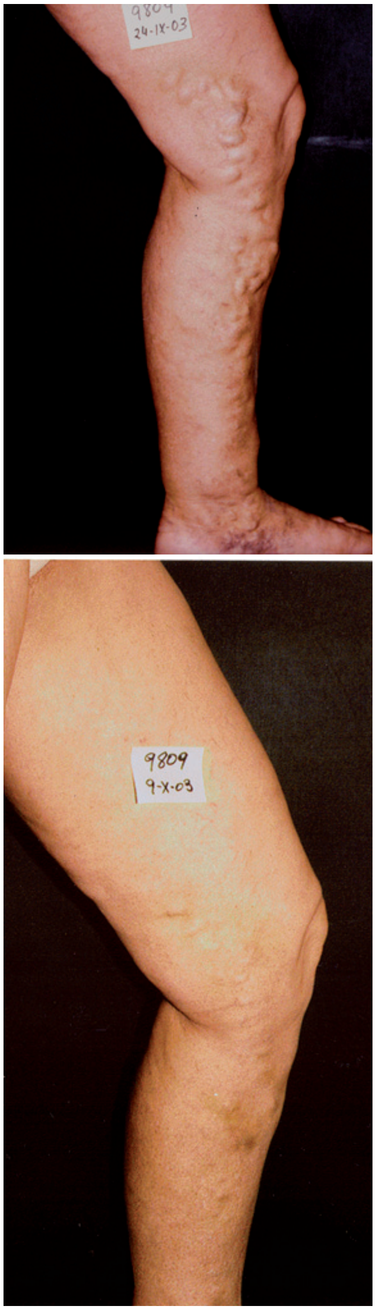

FIGURE 22.3 Involution of superficial tributary varicosities around 15 days after closure of only the proximal segment.

POST-TREATMENT EVOLUTION—PROXIMAL SCLEROSIS

After the reflex vasospasm, and when the patient leaves the clinic, the blood returns to fill the vessel and form a thrombus whose size depends on the dimensions of the treated vein. Subfascial localization, distant from the skin and from saphenous veins in the thigh, favors a post-treatment course with moderate or few inflammatory symptoms. However, proximity of the skin to dilated superficial varicose veins can produce undesirable clinical symptoms and increase the risk of pigmentation.

Voluminous superficial varicose veins must be treated at a lower concentration and always after the size has reduced sufficiently after the closure of the segment proximal to it. The aim of this "proximal sclerosis" is not the stable closure of the saphenofemoral junction or of the proximal source of reflux but rather the involution of distal varicose veins.

The aim is to reduce the size of these veins as much as possible so that they can be treated effectively at minimal concentrations at the next treatment session. In our view, until there is a resolution of the problems of circumferential compression (see later), this is the most appropriate procedure.

The stable occlusion of the saphenofemoral junction was an objective during the early years of microfoam sclerotherapy. To mimic surgical ligation and resection of the saphenofemoral junction, we aimed to close the junction at the common femoral vein, monitoring its progression toward fibrosis and resorption. Nowadays, we pay little attention to the junction, which remains patent, with no reflux in any patient and with no change in the excellent long-term outcomes. This is similar to experience with VNUS Closure© and EVLT.

INTRAVASCULAR EFFECT OF CIRCUMFERENTIAL COMPRESSION

Direct observation using ultrasound has shown that compression stockings of 35 mm Hg have no noticeable effect on the morphology or function of large varicose veins. Since the vein preserves its dimensions, there is nothing to prevent the formation of a thrombus. Even when rolls of gauze or other nonelastic cylinders are placed on the varicose vein and strongly compressed by a bandage of little elasticity (Peha-Haft®; Hartmann), no reduction in the diameter of trunk varicose veins is produced on standing. Thus, the joint application of these compressive measures (i.e., stocking + bandage + nonelastic cylinders) does not occlude the lumen of the vessel.

SELECTIVE COMPRESSION

In order to overcome the inefficacy of circumferential compression on varicose trunk veins in leg, we have developed a device made of flexible inelastic fabric interwoven with two bands of little elasticity. It can be fitted to legs of different diameters using a Velcro®-type fastener, and it

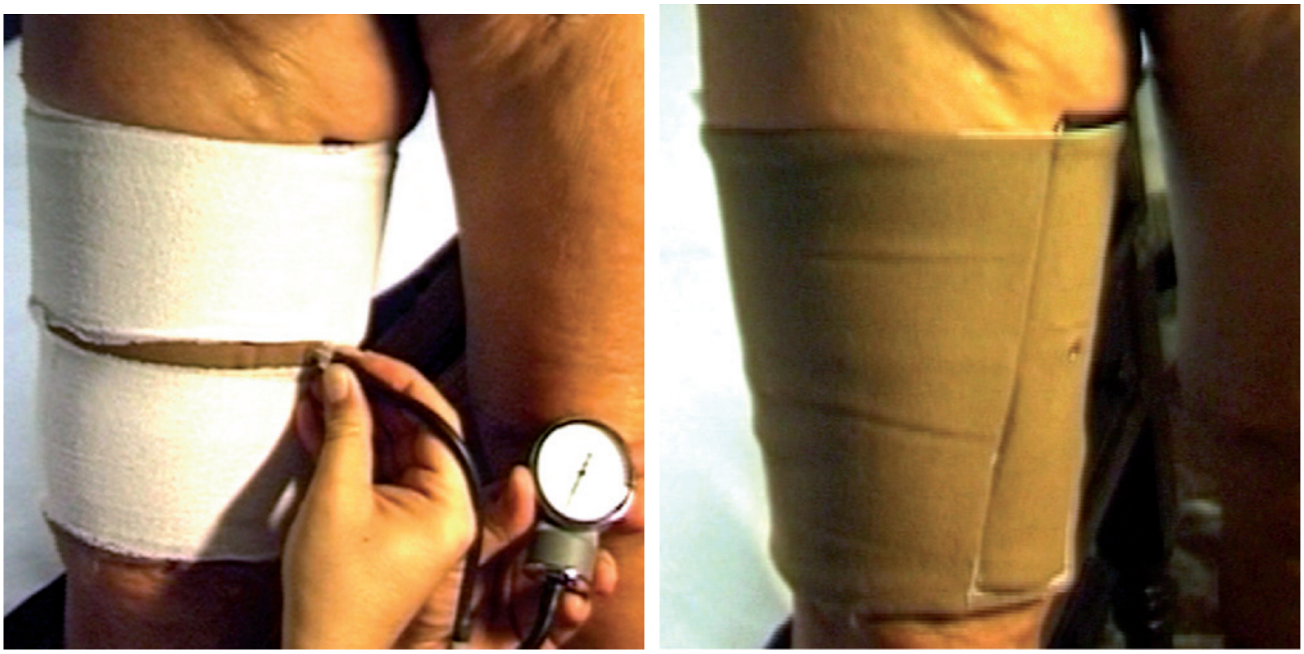

FIGURE 22.4 This device is made of flexible inelastic fabric interwoven with two bands of little elasticity. It contains an inflatable component equipped with a valve. The positional stability of the unit is essential to its effectiveness. Transient vessel occlusion is ineffective.

contains an inflatable component of asymmetric deformability equipped with a valve (see Figure 22.4). It can be used to apply selective pressure to the treated vein. The minimum pressure required to keep the vessels empty is regulated by means of a manometer.

This device is kept in place for around 10 days, until completion of the wound-healing and fibrosis produced by the original action of the sclerosant in the vein. A selective apparatus of this type must be stable, applying a consistent pressure and not shifting its position on the leg (see Figure 22.5).

SAFETY MEASURES IN MICROFOAM SCLEROTHERAPY

The Closed-door Maneuver

The most feared complications of sclerotherapy are intraarterial injection and deep vein thrombosis. The use of color duplex ultrasonography helps to avoid intraarterial injection, and injection of the Great Saphenous at the thigh rules out a possible injection of the femoral artery. At other sites, the use of ultrasound-guided injection and the excellent reports on this issue have reduced the incidence of this complication, although the clinician must always be alert to this danger. Routine is a poor companion in sclerotherapy.

In the sclerotherapy of varicose trunk veins, deep vein thrombosis usually is produced by a coagulation disorder in the patient or by an error in the administration technique (see Figure 22.6). The most frequent site for this complication is in leg muscle veins. However, in our experience treating over 10,000 Great Saphenous veins with microfoam sclerotherapy, we have observed no occlusion of the common femoral vein. Its high flow dilutes the sclerosant and reduces the impact of failures of technique, such as the injection of high concentrations or excessive volumes of microfoam for the size of vessel treated. Nevertheless, at the start of our experience, when the technique was not fully developed, we performed slow injections, letting the microfoam pass through the Great Saphenous vein without taking advantage of the mechanical action of the pneumatic piston. At that time, we observed several thromboses in the common femoral caused by bubbles that floated on the blood with the patient in supine position. These passed to the femoral vein in "Indian file" still loaded with sclerosant, contacting its upper epithelial wall. The limited extent of this thrombosis and its subocclusive nature ensured its rapid lysis in the very few patients with this complication.

The potentially most controversial points in sclerotherapy of the saphenous reflux are perforating veins with direct connection to the DVS: femoral, popliteal, and medial gastrocnemius veins (see Figure 22.7).

The very common type of reinjection carries a high risk of extending the thrombosis of the varicose vein to a more

FIGURE 22.5 Patient after a few days of treatment with the compression device. The positional stability on thigh was good but the compression intensity was inadequate.

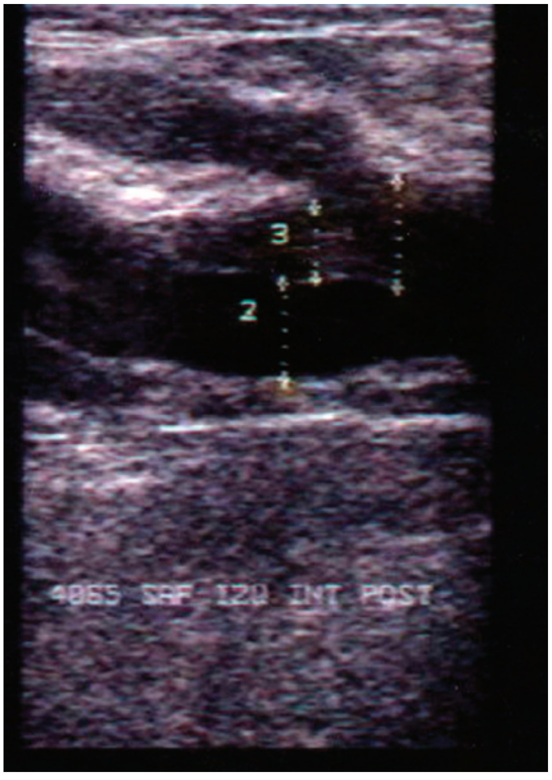

FIGURE 22.6 A partially occlusive thrombosis of common femoral vein caused by an error in technique.

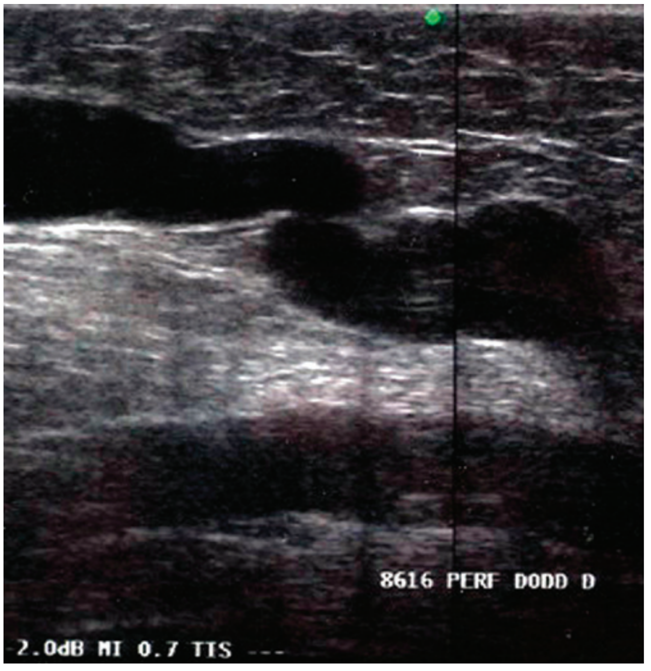

FIGURE 22.7 Perforating veins to the femoral vein carry an increased risk of deep venous thrombosis, and the insertion of the cannula must be carefully controlled to avoid their direct injection.

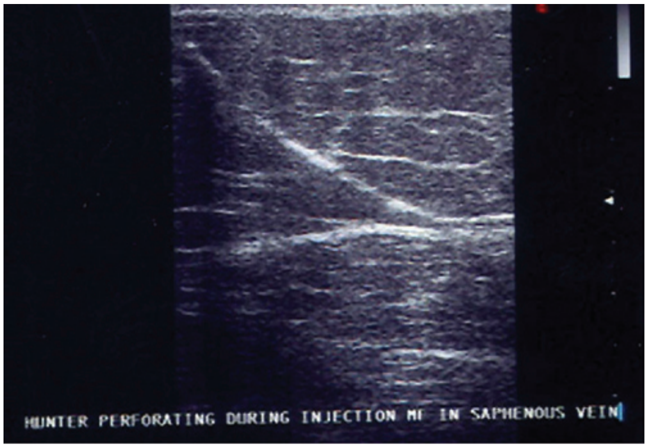

FIGURE 22.8 Passage of microbubbles to the femoral vein during injection of saphenous vein. This situation requires careful duplex monitoring and clearance of the foam particles by foot flexion and extension.

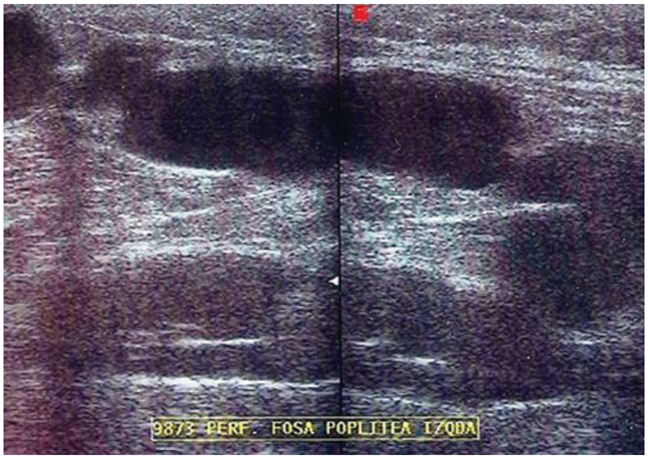

FIGURE 22.9 Perforating veins to the popliteal fossa must be treated while there is compression at the connection point to minimize the volume of foam drained into the deep venous system**.** Varicose vein leading to medial gastrocnemius vein. Nothing prevents the injected sclerosant from exerting its action a little beyond the desired segment.

FIGURE 22.10 Color duplex ultrasonography is used to confirm that dorsal flexion of the foot closes the intramuscular venous segment.

or less extensive segment of the gastrocnemius vein, which would result in thrombosis of the deep venous system, with the possibility of it spreading proximally to popliteal and superficial femoral veins.

We take two precautionary measures to avoid this undesirable action. The first is a dual measure: a reduction in the concentration of sclerosant and a strict limitation of the injected volume to the capacity of the vein to be treated (see Figure 22.8). Injections that exceed this volume and concentrations greater than 0.37% are errors of technique.

The second measure is to close the gastrocnemius vein during and after the injection by taking advantage of the muscle function. We first confirm by ultrasound that these muscle veins are completely closed when the patient is standing and that they remain so while the muscle contraction caused by this position persists, with complete closure of the lumen. In supine position, active dorsal flexion of the foot produces a similar result. If the patient tires, closure by the muscles can be achieved by passive flexion, using the hand of clinician or assistant to exert dorsal pressure on the foot (see Figure 22.9). Active, voluntary contraction of the muscles is more effective, although many patients do not have this ability and must be taught it.

We routinely use dorsal flexion during the injection of any varicose leg vein, checking its effectiveness on ultrasound. If it is not effective, another technique is used (see Figure 22.10).

We also use these novel “closed door” maneuvers during the sclerosis of low perforating veins as a complementary

FIGURE 22.11 Voluminous and complex varicose veins before and after treatment.

measure to the exertion of pressure on the perforating vein itself with finger or ultrasound probe. We must be 100% sure that the sclerosant does not reach the deep venous system in an uncontrolled manner. This combination of safety measures that we have gradually developed and applied in our daily practice has led to a progressive reduction in any complications of this nature.

In our long experience, we have had 22 cases of deep venous thrombosis of leg muscle veins in more than 10,000 patients. In 10 patients, a coagulation disorder was the cause. After the use of these maneuvers we have not observed DVT of muscular veins.

The efficacy of sclerotherapy with microfoam is now beyond doubt. It achieves the elimination of all varicose veins in all patients, with no limitations on the extent, size, site, or morphology of the vessels that can be treated by this method.

The effective safety measures that we have introduced make it the therapeutic approach of choice when the anatomical and functional removal of large and complex pathological varices is indicated (see Figure 22.11).

LONG-TERM EVOLUTION—STABILITY OF OUTCOMES

Our final objective is to make these optimal outcomes stable over the long-term. The Achilles' heel of surgery is the high recurrence rate of varicose veins.[18,19] This is a major limitation of the surgical approach along with the aggressive nature of surgery and its incomplete outcomes.

TABLE 22.1 Compression Requirements of Large Superficial Varicose Veins

Selective
Controllable (with capacity to occlude the vein)
Stable pressure values and position on leg

TABLE 22.2 Measures to Insure Efficacy and Safety

Previous proximal sclerosis
Appropriate concentration of sclerosant
Precise injected volume
Closed-door maneuver
Selective compression of dilated superficial varicose veins

TABLE 22.3 Treatment Strategy

1° Elimination of existing varicose veins
2° Elimination of varicose heritage
One-year active follow-up equals stable outcomes

TABLE 22.4 Future Perspectives

Pharmaceutical grade microfoam
Standard technique

We must warn you that varicose veins often can reappear in legs that were treated only a few months earlier, even when all varicose veins were successfully removed. These recurrences seem to be caused by the development of varicose veins that were not visible at the time of treatment but were nevertheless part of the varicose heritage of the patient. These incompetent veins take the place of those that are removed, maintaining hemodynamic continuity to the end-vessels in leg muscles and ensuring their progression.

Besides sclerotherapy with microfoam, we know of no therapeutic procedure that can remove all types of varicose veins. However, the disappearance of all varicose veins from a given area does not mean that total success has been achieved. Final victory can be claimed only when we can be reasonably sure that we have also eliminated all veins that may constitute a source of recurrence. To this end, an exhaustive color duplex ultrasound study is made at the second treatment session (at 3 to 5 months) and we treat all varicose veins revealed in the leg. Newly formed varicose veins are also identified and treated during follow-up sessions at six, nine, and 12 months. This active follow-up approach achieves the progressive, systematic, and complete

removal of varicose veins that could produce a recurrence and whose suppression is the key to long-term stability of outcomes. These goals cannot be attained by surgery or endoluminal techniques when used alone.

Varicose disease is considered an essentially progressive condition. Nevertheless, application of the correct treatment can markedly reduce the recurrence rate.

Our current working objectives are to continue to improve the technique, accelerating the treatment and making it more comfortable for the patient. The type of compression applied is of critical importance for comfort. Since we have observed no benefits from the application of a strong compression, we use high-quality stockings that exert moderate compression. These Mediven®plus stockings have been well accepted by patients.

The availability of a micronized, homogeneous, and reproducible foam of pharmaceutical grade is crucial, because it would allow us to develop a standard treatment protocol, allowing outcomes obtained by different groups to be compared.

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CHAPTER

23

Ultrasound-Guided Catheter and Foam Therapy for Venous Insufficiency

LUIGI PASCARELLA and JOHN J. BERGAN

INTRODUCTION

Duplex ultrasound sonography represents the best method of evaluation of venous reflux in the lower extremities.[1] This test is noninvasive, generally acceptable to the patient, and inexpensive.[2] It provides direct imaging, localization, and extent of venous reflux with a surprisingly high sensitivity (95%) and specificity (100%).[3] Duplex ultrasound findings have also been confirmed with angioscopic observations of incompetent vein valves in advanced chronic venous insufficiency.[4] As demonstrated by Yamaki, high peak reflux velocities (>30 cm/s), reflux duration greater than three seconds, and an enlarged valve annulus measured by duplex ultrasonography at the SFJ are closely related to angioscopically deformed and incompetent terminal valves (Type III and Type IV valves of Hoshino).[4]

PRETREATMENT ASSESSMENT

The examination should always begin with a complete medical history. Data concerning family and personal venous history, symptoms, clinical findings, and previous venous treatments are collected. Comorbidities, allergies, and pharmacologic history must be documented.[2] The BMI is calculated from the patient's height and weight and should be recorded.

The patient should be examined in a standing position to demonstrate patterns of teleangiectasias, reticular veins, and varicose veins.[5] Cold light transillumination of the skin (vein light) may be used to identify reticular veins, and a handheld Doppler device can verify the presence of reflux in some superficial veins as a screening examination.[5] Thus the three levels of pathologic veins are evaluated. Telangiectasias in the skin are visually inspected, reticular veins are transilluminated with the vein light, and varicosities and the saphenous veins are examined with ultrasound. Clinical data should be integrated into the CEAP classification.[6,7]

EQUIPMENT

The ultrasound duplex scanner should be able to detect blood flow rates as low as 6 cm/sec.[2] This can be done by dedicated high resolution vascular scanners with color and/or power-Doppler functions as well as the pulsed wave Doppler. Linear transducers in the range of 4–7 megahertz are used.[5,8] The inferior vena cava, pelvic veins, and deep veins of the limbs in obese patients may be imaged with 3 megahertz transducers.[1] Linear hockey-stick transducers in the range of 5–12 Mhz can provide a detailed imaging of smaller veins and perforating veins.

With the advances in technology, duplex scanners have become smaller, more transportable, and more operator friendly.[5] Miniaturized devices feature transducers designed with advanced architecture that allow a single probe to image across a greater range of depths within an application and across applications.[5] The transducer for peripheral vascular examinations operates from 10–5 MHz and provides resolution from skin surface to 7 cm in depth.[5] The technology incorporates power Doppler sonography, tissue harmonic imaging, and direct connectivity to a personal computer.[5] Their overall performance is comparable to the more traditional and much larger ultrasound equipment.[5]

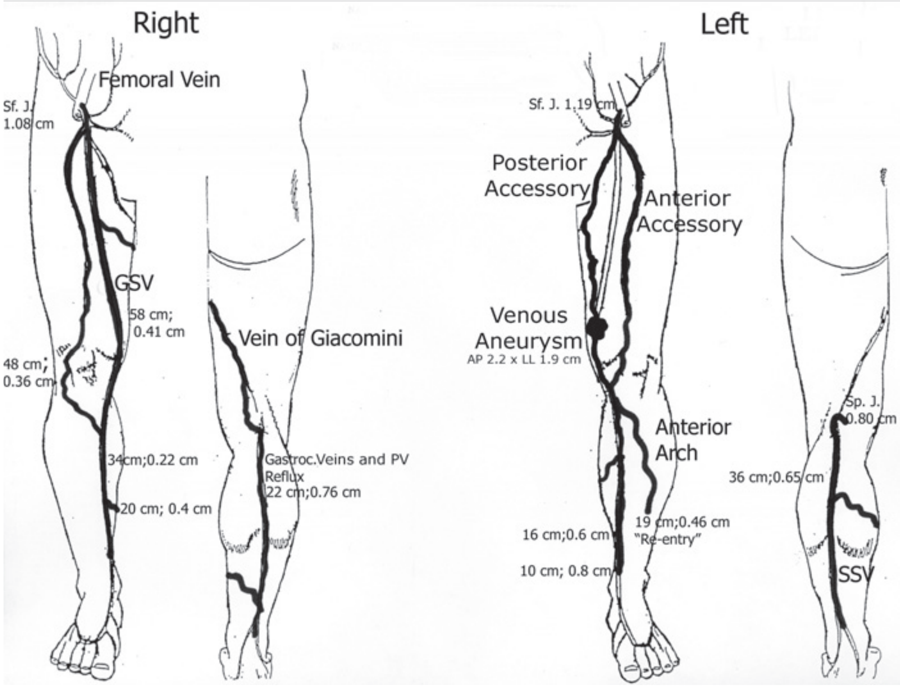

FIGURE 23.1 This data entry form outlines the saphenous veins and the relevant deep veins. Refluxing veins are added in heavy black lines. Location of perforating veins and aneurysms can be added and distance from the floor indicated. Diameters of perforating veins at the fascial level should also be noted.

VENOUS REFLUX EXAMINATION AND VENOUS MAPPING

A detailed US duplex study of the normal and pathologic venous anatomy (reflux) is essential. A clear graphic notation (mapping) of significant vein diameters, anomalous anatomy, superficial venous aneurysms, perforating veins, presence and extent of reflux should always be recorded during the examination (see Figure 23.1).[2,5]

The ultrasound examination is conducted with the patient standing.[9] This position has been found to dilate leg veins maximally and challenges vein valves. Sensitivity and specificity in detecting reflux are increased in examinations performed with the patient standing rather than when the patient is supine.[8,9] Supine examinations for reflux are unacceptable.

The veins are scanned by moving the probe vertically up and down along their course. Duplicated segments, sites of tributary confluence, and large perforating veins and their deep venous connections are identified. Their location measured in centimeters from the floor provides a therapeutic guide. Measurements from the medial malleolus are not as precise. Transverse and longitudinal scans combined with continuous scanning are performed in order to provide a clear mapping of the venous system. Patency usually is assessed by compression of the vein with the transducer.[8] Reflux is detected by flow augmentation maneuvers such as distal compression and release of the thigh and calf or the Valsalva maneuver for only the saphenofemoral junction.[8] Automated rapid inflation/deflation cuffs are cumbersome but may be used for this purpose and offer the advantage of a standardized stimulus.[10–12] Reflux greater than 500 ms is considered pathologic.[9,13]

The diameter of the saphenofemoral junction and femoral vein are recorded for use in judgment for radio frequency VNUS closure© and endovenous laser EVLT treatments.[14–16] Important information also is offered by the diameters of the GSV at mid thigh and distal thigh. Radiofrequency ablation commonly is applied to treat veins from 2–12 mm in diameter.[16] The supragenicular, infragenicular, or immediate subgenicular Great Saphenous vein is often the access point for its laser or radiofrequency ablation.[16,17] Therefore the depth of the GSV in these regions is additional data to be recorded.

Accessory veins by definition run parallel to the GSV in the thigh (see Figure 23.1).[18] It is imperative to map their course accurately and to note their eventual communication with GSV (see Figure 23.1). They are easily confused with the GSV, especially during continuous longitudinal scanning when the saphenous vein appears to leave the saphenous compartment.[18]

The Great Saphenous vein is then scanned in the leg and the thigh so that tributaries to the GSV should be noted (see Figure 23.1).

The diameters of the popliteal vein and the Small Saphenous vein (SSV) are recorded, as well as diameters of the SSV along its course in the leg. Intersaphenous veins should also be identified and the variability in SSV termination carefully recorded.

The venous reflux examination also includes the mapping of exit and reentry perforating veins (PV).[19] PV reflux is detected as outward flow duration greater than 350 ms on the release phase of flow augmentation maneuver (distal compression has higher sensitivity in detecting PVs reflux).[1] Perforating veins should be accurately located in their different locations in the leg. Their position should be measured as distance (cm) from the floor in the extended limb.[18,20]

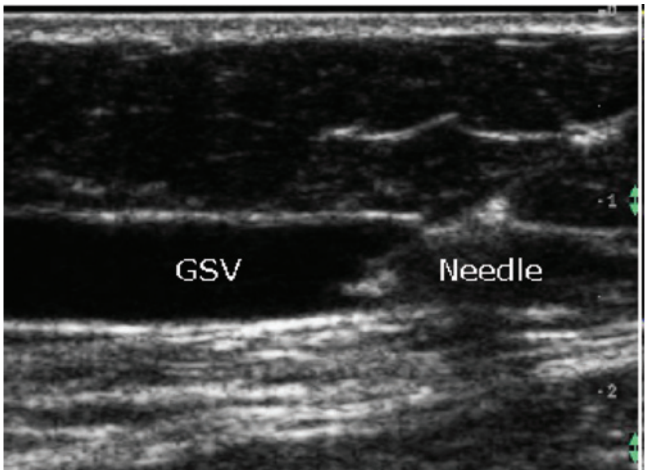

FIGURE 23.2 The Great Saphenous vein is cannulated using the Seldinger technique. The puncturing needle is echogenic and can be easily visualized. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure)

ULTRASOUND MONITORING DURING EVLT AND VNUS CLOSURE© OF THE GSV AND SSV

Thermic coagulation is caused by the application of electromagnetic energy to the endothelial surface of targeted veins.[16,21,22] It has been suggested that the coagulation process in laser treatment is related to the intravascular vaporization of blood (steam) with intimal denudation and collagen fiber contraction. Vein wall thickening and rapid reorganization of the vessel to form a fibrotic cord follow.[21,22] Occlusion usually is visualized within 10 to 20 seconds from the laser or radiofrequency energy application.[22] These techniques have been proven to be safe and effective.[23] Percutaneous introduction of the laser or RF catheter has made formerly extremely invasive therapy (SFJ ligation and GSV stripping) more acceptable to the patient in terms of post treatment pain, number of cutaneous incisions, and post-procedural disability.[15,16]

Before the procedure, it is always recommended to rescan the patient for better identification of the venous segment to cannulate. In this preparatory phase some anatomic landmarks have to be clearly recognizable:

1. Femoral vein
2. Saphenofemoral junction
3. Saphenous compartment
4. Great Saphenous vein
5. Small Saphenous junctional anatomy

Introduction of the introducer sheath is performed percutaneously using the Seldinger Technique. The supragenicular saphenous vein is usually the access point of choice (see Figure 23.2).[17] The intraluminal position of the sheath is ascertained by aspiration of nonpulsatile venous blood. The sheathed laser fiber or a 6 or 8 F VNUS catheter is advanced to a point just distal to the entrance of the epigastric vein.[17] Position of the laser fiber is confirmed by direct visualization of the red aiming beam and that of the VNUS catheter by ultrasound (see Figures 23.3 and 23.4).[16]

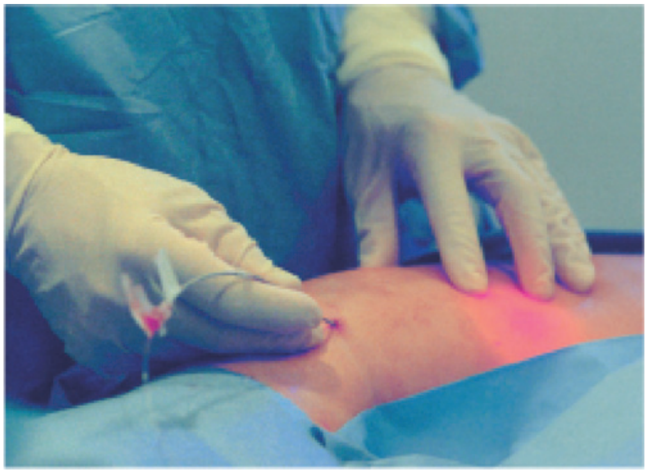

FIGURE 23.3 The laser catheter is advanced proximally toward the saphenofemoral junction. Position of the laser fiber is confirmed by direct visualization of the red aiming beam through the skin. (Adapted from Navarro L, Min RJ, Bone' C. Endovenous laser: A new minimally invasive method of treatment for varicose veins: Preliminary observations using an 810 nm diode laser dermatologic surgery, Volume 27, 2:117. February 2001)

The catheter or sheath appear as a hyperechoic line in the GSV lumen.[14,15] Its placement must be precisely at the SFJ 1 cm distal to the epigastric vein (see Figure 23.4).[16]

Administration of the tumescent anesthesia into the saphenous compartment is monitored by ultrasound.[17] The vein is seen as "floating" in an echogenic sea of the anesthetic solution (see Figure 23.5). It is always wise to recheck

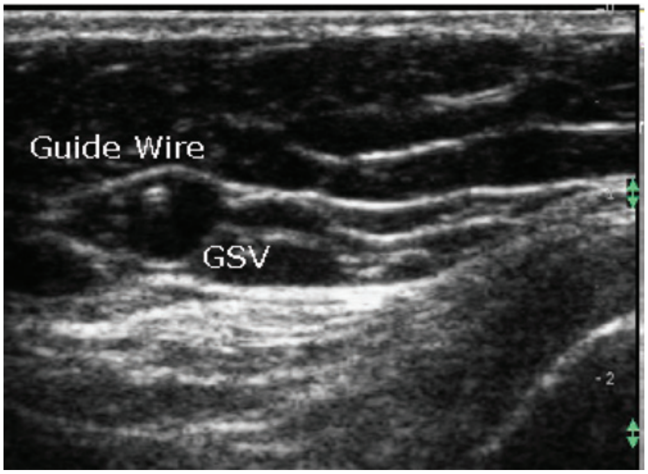

FIGURE 23.4 Position of the guidewire and radiofrequency catheter is monitored by ultrasound visualization. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure.)

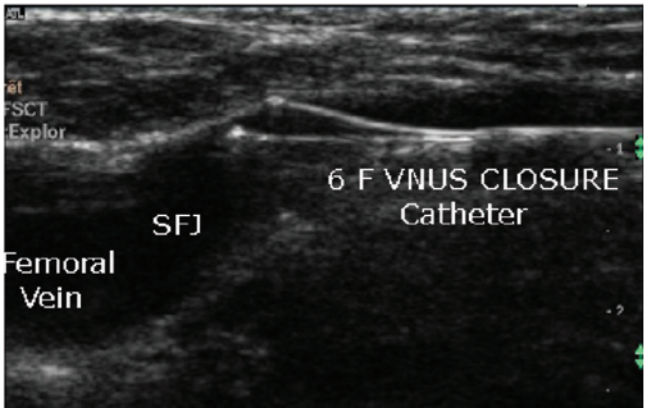

FIGURE 23.6 The ablation starts at saphenofemoral junction and proceeds in a distal direction. It is always wise to recheck the catheter position at SFJ prior the application of the energy. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure.)

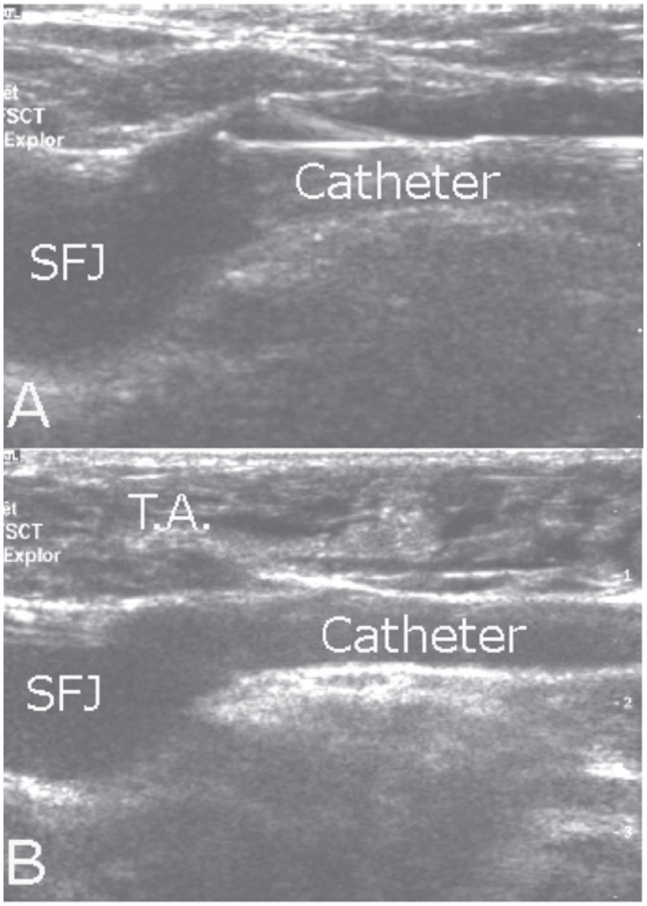

FIGURE 23.5 Administration of the tumescent anesthesia into the Saphenous Compartment is monitored by ultrasound. SFJ: Saphenofemoral Junction; T.A.: Tumescent Anesthesia. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure.)

the catheter position at SFJ prior the application of the energy (see Figure 23.6).[22]

The ablation starts at saphenofemoral junction and proceeds in a distal direction.[16] Successful obliteration is confirmed by contraction of the saphenous vein to a residual diameter of <2 mm.[16] Patency of the common femoral artery and vein are confirmed by ultrasound (see Figure 23.7). A thrombus may be seen as a hyperechogenic core in the vessel (see Figure 23.7b).[15,24]

Early post treatment duplex scanning should be performed. Evidence of a protruding thrombus from the saphenous vein into the femoral vein should be anticipated (see Figure 23.8).[24] Evidence of a noncompressible GSV with thickened walls and absence of flow on color ultrasound analysis are signs of successful obliteration (see Figure 23.9).[9]

ULTRASOUND MONITORING DURING SCLEROFOAM ABLATION OF VARICOSE VEINS

Advent of foam sclerotherapy has added a new tool for the treatment of chronic venous insufficiency. Sclerosant agents provoke endothelial damage by several mechanisms.[25] They change either the surface tension of the plasma membrane (detergents) or the intravascular pH and osmolarity. The final result is a chemical fibrosis of the treated vessel.[25]

Sclerosing foams (SF) are mixtures of gas with a liquid solution with surfactant properties. In 1993, Cabrera proposed the use of SF, made of sodium tetradecyl sulfate or polidocanol in the treatment of varicose veins.[26] One of the intrinsic limits of liquid sclerosants in the treatment of

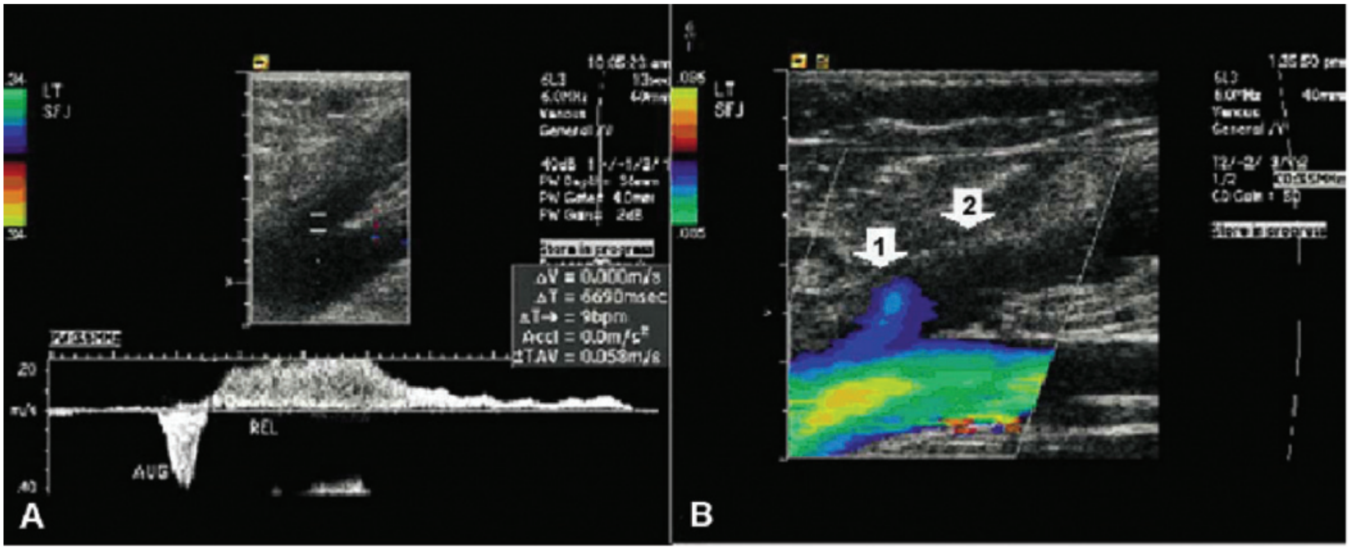

FIGURE 23.7 Duplex examinations (longitudinal views) of the Great Saphenous vein (GSV) at the saphenofemoral junction (SFJ). **A**. Pretreatment scan demonstrated an incompetent SFJ after augmentation. **B**. Intraoperative color duplex interrogation showed successful occlusion of the GSV with a patent, 3-mm proximal stump (arrow 1) and absence of flow within the treated segment (arrow 2). (Adapted from Puggioni A, Kalra M, Carmo M, Mozes G, Gloviczki P. Endovenous laser therapy and radiofrequency ablation of the great saphenous vein: Analysis of early efficacy and complications, J Vasc Surg. 2005. Sep;42(3): 488–493.)

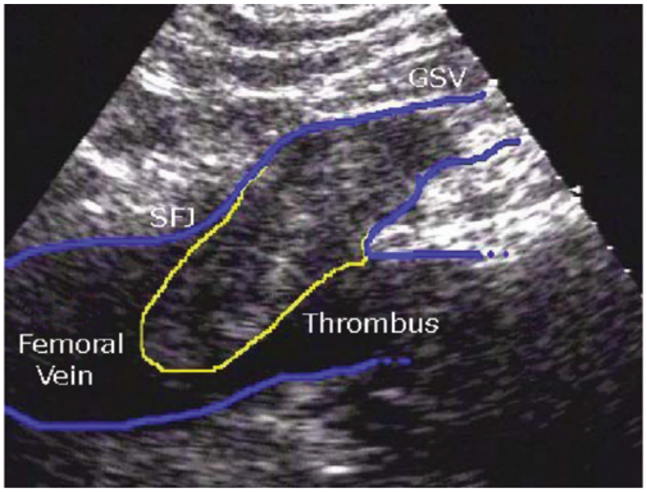

FIGURE 23.8 Early post treatment duplex scanning should be performed. Evidence of a protruding thrombus from the saphenous vein into the femoral vein should be looked for. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure)

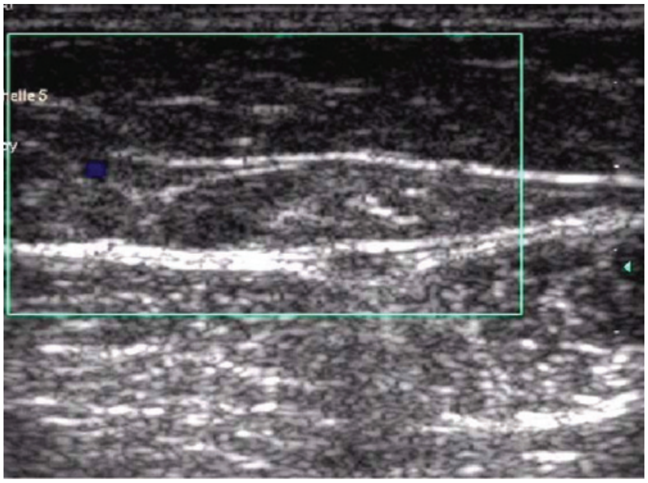

FIGURE 23.9 Evidence of a noncompressible GSV with thickened walls and absence of flow on color ultrasound analysis are signs of successful obliteration. (Adapted from Pichot O, Atlas of Ultrasound Images, Copyright VNUS® Closure)

varicose veins is dilution by the bloodstream with reduction of their efficacy.[27] Also, they are rapidly cleared by the moving bloodstream. Sclerosing foams do not mix with blood and instead remain in the vessel, continuing to strip the endothelium.[27] This persistence of the agent in the vessel causes an increased contact time with the intimal surface. Foam preparation is remarkably simple.[27] The Tessari 3-way stop-cock method is the most commonly used.[27,28]

As in electromagnetic ablation, the treatment starts with clear ultrasound mapping. Varicose veins can be accessed by the placement of 25 G butterfly needle, or the Great Saphenous or the Small Saphenous vein can be directly cannulated with an angiocath, an echogenic Cook® needle, or a 25 G butterfly.[27,29,30] Most descriptions of the technique explain direct ultrasound-guided access to the saphenous vein.[27,31] In contrast, we achieve a satisfactory and rapid

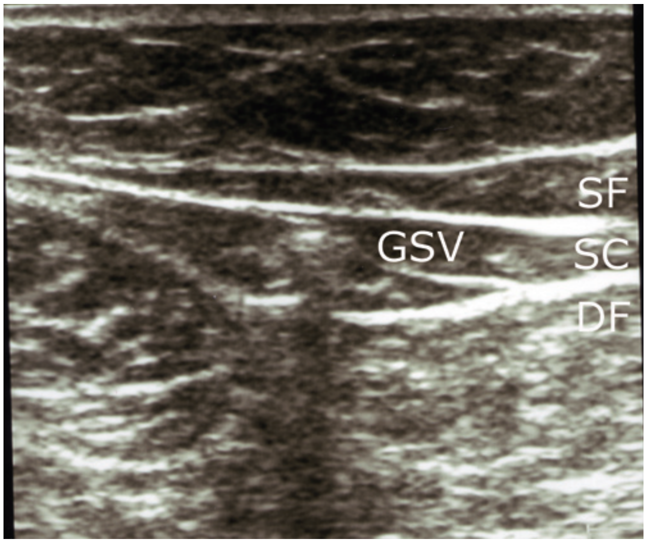

FIGURE 23.10 Foam functions as an efficient ultrasound contrast medium because of its air content. Its injection can be easily monitored. Its US appearance is that of a solid hyper-echogenic core with an acoustic shadow projected on the tissue below.

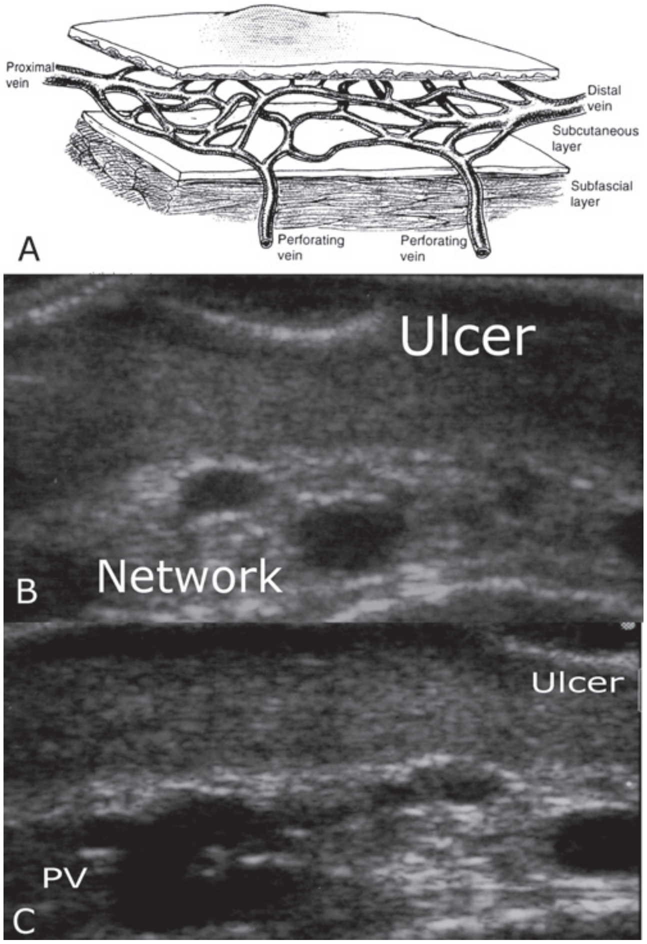

FIGURE 23.11 Ultrasound sonography has confirmed the presence of a tangled network of varicose veins of small caliber, reticular varices, and incompetent perforating veins under lipodermatosclerotic plaques and under venous ulcers. These are the tagets for successful foam sclerotherapy.

obliteration of the GSV and SSV by cannulating a peripheral varicosity.[30] Although the saphenous vein cannot be cannulated with a catheter by way of a varicosity because of its angle of connection, there is no such obstacle to the flow of foam.

Foam functions as an efficient ultrasound contrast medium because of its air content. Its injection can be easily monitored. Its US appearance is that of a solid hyperechogenic core with an acoustic shadow projected in the tissue below (see Figure 23.10).

Foam is introduced into a varix or the saphenous vein with the patient supine. As the foam reaches the SFJ as monitored by ultrasound, compression of the SFJ or the SPJ is effected in order to reduce flowing of foam into the systemic circulation.

Vasoconstriction and vasospasm can be induced by intermittent compression of the vein by the ultrasound transducer and by elevating the limb. This minimizes the blood content of the saphenous vein and its connected varices. Foam will be seen by ultrasound to flow distally in the elevated limb. It flows selectively through incompetent valves and is effectively blocked by competent valves. These maneuvers have the effect of prolonging the action of the foamed sclerosant on the intima, improving the efficacy of the entire treatment. The femoral, popliteal, and deep veins of the leg are scanned throughout the entire procedure. Foam particles are washed out of deep veins such as the gastrocnemius or tibial veins by flexion-extension maneuvers of the foot. Quick movements of dorsiflexion of the foot completely clear the deep veins. Despite much worry about the problem, major thrombotic events in the femoral and popliteal veins rarely have been described with use of sclerofoam. In a study of over 1,200 sclerotherapy sessions, over half of which involved foam, only a single femoral vein thrombus was encountered.[32]

Thromboses of the gastrocnemius, tibial, and peroneal veins have been reported only occasionally.[30,33] Intraarterial injections are uncommon because of monitoring the foam treatment of severe CVI.[30,33] Ultrasound sonography has confirmed the presence of a tangled network of varicose veins of small caliber, reticular varices, and incompetent perforating veins under lipodermatosclerotic plaques and under venous ulcers (see Figure 23.11).[30] Ultrasound monitoring is used to confirm the fact that these vessels are filled with foam during the therapeutic maneuvers. Ultrasound guidance is also used in treatment of incompetent perforating veins by direct cannulation and controlled injection of

the SF under direct visual control.[27] More often superficial peripheral veins can be directly injected with obliteration of the inciting perforator and the network of the incompetent veins.

DISCUSSION

Compression therapy and surgery have been the cornerstone of CVI treatment for years and they are still useful. New minimally invasive techniques such as radiofrequency ablation of saphenous veins, EVLT, and GSV and SSV ablation with Sclerofoam of superficial varicose veins have been demonstrated to be safe, effective, and more acceptable to the patient.[16] The contribution of ultrasound in general and duplex technology in particular has given reliability to the diagnosis of CVI and has enhanced the development of these minimally invasive therapies. Intraprocedural and postprocedural US duplex ultrasound monitoring offers the best control of the entire procedure with early prevention of complications (thrombosis of deep veins) and eventual minimalization of failure.

CONCLUSION

US duplex ultrasound is essential in every phase of the CVI patient care. Experience, critical thinking, uniform testing, and insight in the pathology are necessary to achieve satisfactory results.

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C H A P T E R

24

Principles of Treatment of Varicose Veins by Sclerotherapy and Surgery

STEVEN E. ZIMMET

Varicose veins may be of cosmetic concern to patients, and may cause a variety of symptoms, signs, and sequelae. As physicians interested in venous disease, we know from daily practice that venous insufficiency significantly impacts our patients' quality of life (QoL). There are now data to substantiate our clinical impression[1–5] and to indicate that QoL can be improved with intervention in these patients.[3,6,7]

Treatment for venous disease has undergone rapid innovation in the last decade. Despite these advances varicose vein treatment is not curative. Superficial venous insufficiency is a chronic disorder that should be viewed more like a medical than surgical condition.[8] Nonetheless, it is apparent that outcomes can be optimized when certain principles of treatment are followed. This chapter will discuss the development of the principles that are generally accepted today.

A history, physical, and duplex ultrasound examination are prerequisites for adequate treatment of varicose veins. Treatment of varicose veins, except when addressed by conservative or pharmacologic measures, should eliminate sources of venous hypertension. These can be gravitational, as with axial vein reflux, or hydrodynamic, due to increased compartmental pressure during muscular contraction.[9] Therefore, rational treatment depends on the delineation of sources of reflux between the deep and superficial system along with the extent of truncal and tributary incompetence. An individualized treatment plan is developed based on the findings of the evaluation and on the goals of the patient. Treatment goals may include cosmetic improvement, relief of venous-related symptoms (such as leg heaviness, fatigue, pruritus, night cramps, etc.), management of venous-related sequelae (such as edema, dermatitis, lipodermatosclerosis, ulceration, thrombophlebitis, and external bleeding), prevention of complications and control of the disease process. Treatment risks, benefits, and alternatives should be discussed with the patient when determining a treatment plan. Factors to consider and discuss include:

- Efficacy of treatment alternatives
- Durability of results
- Cosmetically acceptable results
- Risk of complications
- Ease of recovery
- Cost

Saphenous vein reflux is the underlying primary abnormality in the majority of cases of superficial venous insufficiency. Thus, approaches to dealing with saphenofemoral junction and saphenous truncal incompetence have dominated the thinking of phlebologists. Trendelenburg described saphenofemoral junction ligation alone, without stripping of the incompetent saphenous vein, in the 1890s. The advantages of this technique over ligation and stripping are still extolled today.[10] Advocates of this approach have pointed out that it preserves the saphenous trunk for possible future use as a bypass graft,[11] and avoids the risk of saphenous nerve injury.[12] High ligation alone is also less invasive, quicker, and simpler to perform, and associated with an easier recovery compared to vein stripping. Unfortunately, the shortcomings of ligation alone outweigh its advantages. Although it is true that such treatment routinely "spares" the saphenous trunk,[13] the use of a diseased saphenous vein as a conduit has been associated with an increased risk of graft failure.[14] Most importantly there is no longer any question that high ligation alone is coupled with persistent reflux in the saphenous trunk.[15,16] Bergan concluded 15 years ago that "duplex scanning confirms the fact that high ligation alone allows persistence of distal reflux after surgical intervention."[17] It is not surprising that varicose recurrence is

significantly reduced[16,18,19] and the reoperation rate is 60 to 70% less if the saphenous vein is stripped vs. ligation alone.[20,21] Regarding the clinical bottom line, more patients were completely satisfied (65 versus 37%) and were recurrence-free (65 versus 17%) when the great saphenous vein (GSV) had been stripped compared with saphenofemoral ligation alone ($P < 0.05$ and $P < 0.001$, respectively).[22] The authors concluded that the addition of GSV stripping to saphenofemoral ligation and multiple avulsions results in a better overall outcome. Recurrence or residual communication with the junction in the groin was found in 80% of patients after ligation alone, and 34% of limbs also had mid-thigh perforator incompetence via the unstripped GSV.[23] As Neglen concluded, stripping of the GSV of the thigh is essential to minimizing recurrence due to redevelopment of incompetent communication with the saphenofemoral confluence and due to thigh perforator incompetence.[24]

Another vein sparing technique is external banding, which aims to restore proximal valvular competence of the GSV. A small number of reports suggest this approach may be efficacious.[25,26] However, these procedures are not widely practiced or accepted. Conservative hemodynamic treatment of incompetent varicose veins in ambulatory patients (*Cure Conservatrice et Hemodynamique de Insufficience Veneuse en Ambulatoire*, CHIVA) is another conservative technique that seeks to normalize venous pressure by ligation of points of venous reflux at reentry perforators. It requires a difficult ultrasound mapping of the venous system. Disconnection of the flow to reentry perforators, without high ligation of the saphenofemoral junction, has been reported to successfully suppress GSV reflux.[27] A different group found recurrence of GSV reflux in 92% at three years.[28] These authors concluded that "elimination of reflux in the GSV after the interruption of insufficient collaterals is only temporary." It's revealing that a survey of vascular surgeons in France, where CHIVA was developed, found this form of venous surgery to be practiced by only 0.3% of the 280 respondents.[29]

At the other end of the spectrum, stripping of the entire saphenous from ankle to groin, along with stab avulsion of varices, has been practiced. This was advocated because it was assumed that reflux extended to the ankle in most patients. However, in a duplex study on over 500 legs the most common pattern was saphenous reflux from the groin to the knee (43.4%), with reflux reaching the ankle in only 1%.[30] The authors concluded that clinically diagnosed GSV reflux in the lower leg usually represented tributary varices, which joined the saphenous vein proximally. These findings, along with the high incidence of saphenous neuralgia from groin to ankle stripping, explain recommendations for "short" stripping of the GSV from groin to just below the knee. Note that such stripping would avoid the risk of saphenous nerve injury yet would disconnect mid-thigh perforators, which as noted earlier are a common cause of recurrence when ligation alone is employed.

It is important to note that recurrence is common even after ligation and stripping of the saphenous. Inadequate surgery of the saphenofemoral junction has been claimed to be an important factor contributing to recurrence.[31] Meticulous dissection of the junction, taking each tributary back beyond each primary and even secondary tributary when possible, was advocated.[32] Whereas progression of disease is another mechanism that explains some cases of recurrence, neovascularization around the junction has been established to be an important cause of recurrence after venous surgery.[21,33] In fact, neovascularization has been reported as the principal cause of recurrence,[19] with neovascular channels of variable size, number, and tortuosity accounting for the reflux to recurrent varicosities in the vast majority of cases.[34] Although some have expressed doubt as to the veracity of true neovascularization, there is clear histological evidence that neovascularization is a cause of recurrent varicose veins.[35] Early reports suggest that endovenous ablation techniques are associated with a very low incidence of neovascularization. It may be that by avoiding groin dissection and by preserving venous drainage in normal junctional tributaries the development of neovascularization is largely avoided.[36,37]

In addition to junctional incompetence, another source of deep to superficial incompetence is via perforating veins. We've already noted the role of thigh perforators in recurrence, primarily when the saphenous trunk is not ablated. However, ablation of the GSV doesn't address lower leg perforator incompetence directly since most of these perforators don't drain into the GSV itself. Nonetheless, patients with superficial and perforator vein incompetence and with a normal deep venous system experienced significant improvement in APG-measured hemodynamic parameters and clinical symptom score after superficial ablative surgery alone.[38] The authors suggested that treatment of perforator veins can be reserved for patients with persistent incompetent perforator vessels, abnormal hemodynamic parameters or continued symptoms after superficial ablative surgery. Another study corroborated these results, but found that saphenous surgery alone failed to correct perforator reflux when there was coexistent deep venous reflux or if superficial reflux persisted postoperatively.[39] The resolution of perforator reflux following treatment of superficial venous disease is similar to the improvement in deep venous hemodynamics that has been observed after ablation of superficial reflux,[40,41] and is probably due to a reduction in venous overload.

Currently accepted principles of treatment of varicose veins serve to maximize outcomes from a hemodynamic and patient standpoint while minimizing the risk of recurrence. Appropriate treatment of varicose veins begins with an accurate assessment of the underlying venous pathology and identification of sources of venous hypertension. The aims of treatment include elimination of the incompetent connections between the deep and superficial systems as well as

the obliteration of pathways of venous incompetence and incompetent varicose veins. It is clear that recurrence is reduced if the incompetent segment of the saphenous trunk is ablated. Duplex ultrasound examination reveals that the GSV is often competent and of much smaller diameter below a site of saphenous-varicose tributary connection, usually located in the thigh or proximal lower leg. Ablation of the entire GSV, from groin to ankle, is almost never required. It appears that avoiding groin dissection and preserving normal junctional drainage may prevent the development of neovascularization, an important cause of recurrence following ligation and stripping. Thus endovenous treatments, including endovenous laser, radiofrequency ablation, and foam sclerotherapy, may yield the benefits of ablation of the incompetent saphenous trunk while minimizing recurrence due to neovascularization. Causes of recurrence following these endovenous treatments appear to be due primarily to failure to fully ablate incompetent truncal veins (failure or recanalization) or due to progression of disease.

There is a pervasive trend in medicine toward minimally invasive treatments. The approach to venous disease is no different. Ablating only incompetent venous segments is in keeping with this approach. The application of the principles of tumescent anesthesia to venous treatments,[42] along with the development of endovenous treatments, offers the possibility of treating the vast majority of patients with superficial venous insufficiency in-office without general anesthesia or surgical incisions, while maximizing outcomes and minimizing recurrence.

Superficial venous disease is a chronic disorder. Patient education regarding preventative measures is appropriate regardless of which treatments are performed. These measures include regular aerobic exercise and the use of compression stockings.

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C H A P T E R

25

Inversion Stripping of the Saphenous Vein

JOHN BERGAN

One of the cornerstones of surgery for varicose veins is removal of the Great Saphenous vein (GSV) from the circulation. This can be done using minimally invasive techniques described elsewhere in this volume, but specific indications for performing saphenous surgery remain. These are largely institutional and geographic but they justify the following exposition.

Indications for intervention in primary venous insufficiency are listed in Table 25.1. Often, it is the appearance of telangiectatic blemishes or protuberant varicosities that stimulates consultation. Ultimately, this may be the only indication for intervention.[1]

Characteristic symptoms include aching, pain, easy leg fatigue, and leg heaviness, all relieved by leg elevation,[2] and worsened on the first day of a menstrual peritod. Other indications for intervention for venous varicosities include superficial thrombophlebitis in varicose clusters, external bleeding from high-pressure venous blebs, or advanced changes of chronic venous insufficiency such as severe ankle hyperpigmentation, subcutaneous lipodermatosclerosis, atrophie blanche, or frank ulceration. Symptoms are frequent throughout the CEAP Classes 1 through 6. Clinical Disability Scores parallel the clinical classification.[3]

Objectives of treatment should be ablation of the hydrostatic forces of axial reflux and removal of the effects of hydrodynamic forces of perforator vein reflux. The latter can be accomplished by removal of the saphenous vein in the thigh and the varicose veins without specific perforating vein interruption. In France, the two most performed procedures recently were, respectively, high ligation + saphenous trunk stripping + tributary stab avulsion (71.9%) and high ligation + saphenous trunk stripping (17.3%). Isolated phlebectomy was done in 5.6%, high ligation + tributary stab avulsion + saphenous trunk preservation 2.8%, isolated high ligation 2.2%.[4]

Ligation of the saphenous vein at the saphenofemoral junction has been practiced widely in the belief that this would control gravitational reflux while preserving the vein for subsequent arterial bypass.[5] It is true that the saphenous vein is largely preserved after proximal ligation. Unfortunately, reflux continues and hydrodynamic forces are not controlled. Less reflux persists when the long saphenous vein has been stripped.[6] There is a better functional outcome after stripping and fewer junctional recurrences.[7] Randomized trials show efficacy of stripping compared to simple proximal ligation.[8–11]

Earlier comparisons of saphenous ligation versus stripping were flawed by today's standards. Subjective evaluation was the only means of measuring outcome for a time.[12] Duplex scanning came into use, verifying that stripping was superior to proximal ligation; this fact was supported by PPG.[13] Despite those facts, it was acknowledged that the period of disability after stripping was greater than that after simple ligation.[14] In attempts to decrease disability and improve efficacy, high tie was added to saphenous vein sclerotherapy, but foot volumetry showed that radical surgery, including stripping produced superior results.[15]

Ultimately, attention became focused on saphenous nerve injury associated with ankle to groin stripping.[16] It was concluded that nerve injury was reduced by groin to ankle stripping (see Figure 25.1).[18,19] Preservation of calf veins by stripping to the knee was shown to reduce nerve injury and did not adversely affect early venous hemodynamic improvement.[20] This fact is contraintuitive, and the subject deserves further study.[21]

Attempts to reduce nerve injury and simultaneously clean up varicose vein surgery led to use of the hemostatic

TABLE 25.1 Varicose Veins: Indications for Intervention

General appearance
Aching pain
Leg heaviness
Easy leg fatigue
Superficial thrombophlebitis
External bleeding
Ankle hyperpigmentation[1]
Lipodermatosclerosis
Atrophie blanche
Venous ulcer

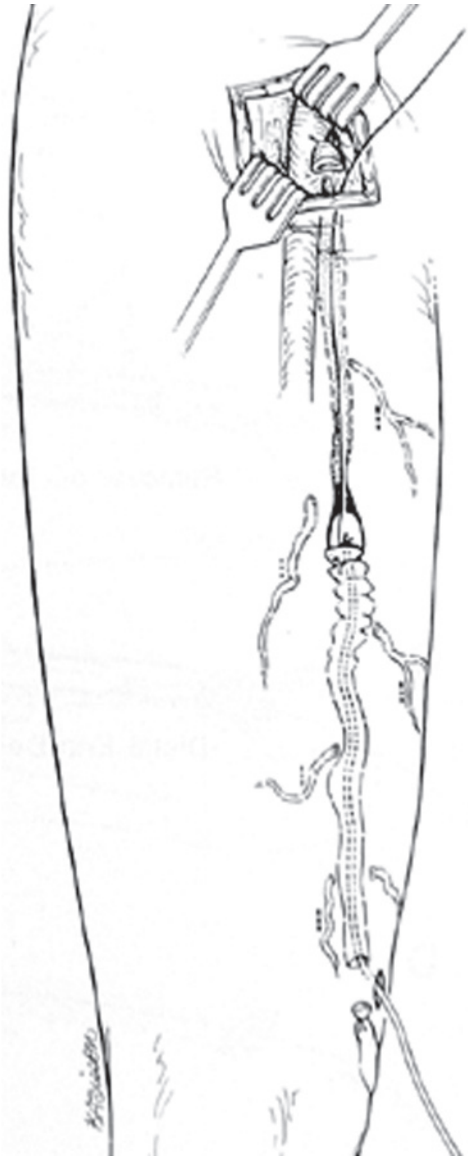

FIGURE 25.1 In an early attempt to improve the results of varicose vein surgery, saphenous stripping, the obturator was drawn from above downward and then retrieved through the groin incision. Postoperative appearance was improved but disability from pain, ecchymosis, and hematoma continued.

tourniquet. In a study with level 1 evidence, it was shown that use of a hemostatic cuff tourniquet during varicose vein surgery reduces perioperative blood loss, operative time, and postoperative bruising without any obvious drawbacks.[22] Villavicencio summarized this advance, saying,[11] "This technique represents a welcome alternative to the bloody, tedious, and time-consuming traditional varicose vein surgery of the past. Complex venous surgery for extensive varicose veins of the extremities can be safely and expeditiously performed under controlled ischemia. It should be the technique of choice."[23]

Recurrent varicose veins after surgery are acknowledged to be a major problem for patients and society.[24] Traditionally, it was thought that the most common reason for varicose recurrence was failure to perform an adequate saphenofemoral junction dissection (see Figure 25.2), or to correctly identify the saphenous vein for removal.[25] Duplex scans have clarified this situation and instead of technical error, some investigators are convinced that new vessel growth contributes to recurrent varicose veins.[26] In particular, incomplete superficial surgery, at the saphenofemoral and saphenopopliteal junctions, is a less frequent cause of recurrent disease, and neovascular reconnection and persistent abnormal venous function are the major contributors to disease recurrence.[27]

PREOPERATIVE PREPARATION

Over the years, much space has been given to clinical examination of the patient with varicose veins. Many clinical tests have been described. Most carry the names of now-dead surgeons who were interested in venous pathophysiology. This august history notwithstanding, the Trendelenburg test, the Schwartz test, the Perthes test, and the Mahorner and Ochsner modifications of the Trendelenburg test essentially are useless in preoperative evaluation of patients today.[28]

The clinical evaluation can be improved by using handheld Doppler devices. However, preoperative evaluation is best performed by means of duplex scanning and a focused physical examination. Our protocol for duplex mapping of incompetent superficial veins has been published.[29] Although many cite cost considerations as a reason for omitting duplex evaluation, we believe that duplex scanning for venous insufficiency is in fact both simple and cost effective. Duplex mapping defines individual patient anatomy with considerable precision and provides valuable information that supplements the physician's clinical impression.

Three principal goals must be kept in mind in planning treatment of varicose veins: 1) the varicosities must be permanently removed and the underlying cause of venous hypertension treated; 2) the repair must be done in as

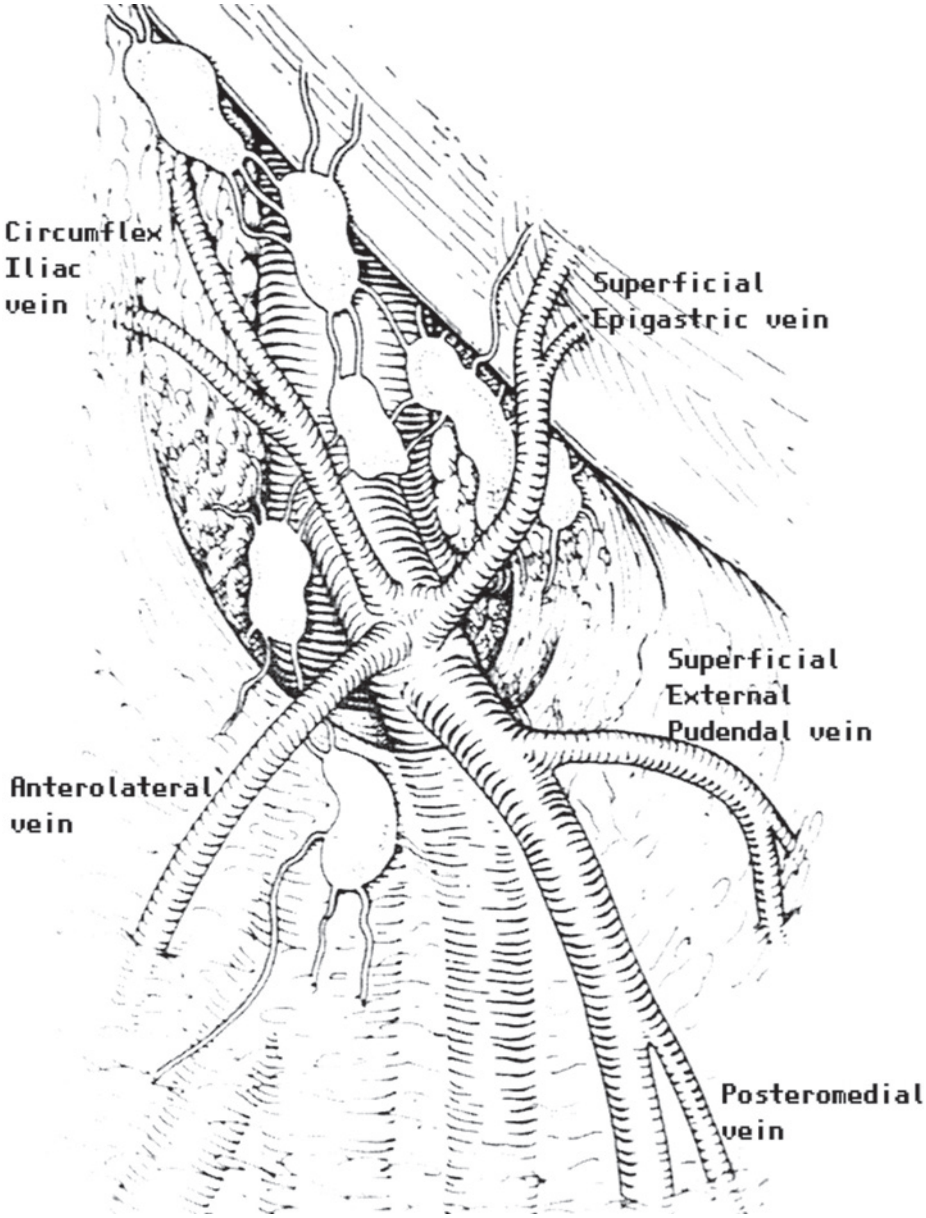

FIGURE 25.2 In the past, a proper groin dissection consisted of laying out each of the named saphenofemoral junction tributaries and dissecting them back beyond their primary tributaries. Now, this is acknowledged by most to be the strongest stimulus to neovascularization.

cosmetic a fashion as possible; 3) complications must be minimized.

Current practice of treating the source of venous hypertension, the saphenous vein alone either by EVLT or VNUS technology, is inadequate. The patient's complaint, the varicose veins, must be addressed. This is as important as the physician's knowledge that the sources of venous hypertension must be addressed.

To speak of permanent removal of varicosities implies that all potential causes of recurrence have been considered and that surgery has been planned so as to address them. There are four principal causes of recurrence of varicose veins, of which three can be dealt with at the time of the primary operation.

One cause of recurrent varicosities is failure to perform the primary operation in a correct fashion. Common errors include missing a duplicated saphenous vein and mistaking an anterolateral or accessory saphenous vein for the greater saphenous vein. Such errors can be eliminated by careful and thorough groin dissection. Accordingly, failure to do a proper groin dissection has long been held to be a second principal cause of recurrent varicose veins. It is now known,

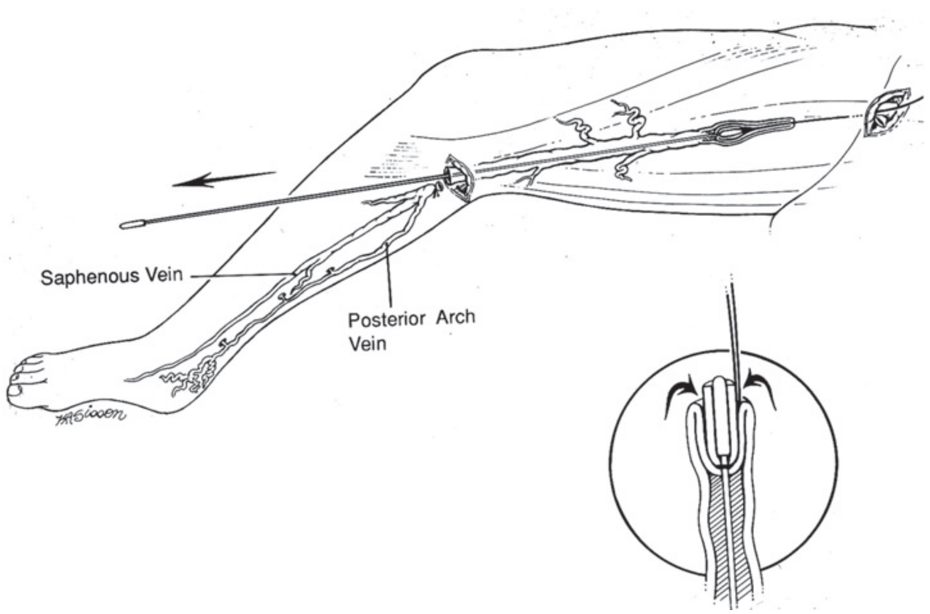

FIGURE 25.3 Inversion stripping of the saphenous vein was an important step forward in minimizing soft tissue trauma while accomplishing the principal objective of ablating hydrostatic venous hypertension by removing saphenous reflux. Tearing of the vein during its removal flawed its performance.

however, that such dissection causes neovascularization in the groin, leading to recurrence of varicose veins.[30] A third cause of recurrent varicosities is failure to remove the greater saphenous vein from the circulation. As mentioned earlier, reasons often cited for this failure is the desire to preserve the saphenous vein for subsequent use as an arterial bypass. It is clear, however, that the preserved saphenous vein continues to reflux and continues to elongate and dilate its tributaries. This produces more and larger varicosities. A fourth cause of recurrent varicosities is persistence of venous hypertension through nonsaphenous sources—chiefly, perforating veins with incompetent valves. Muscular contraction generates enormous pressures that are directed against valves in perforating veins. Venous hypertension induces a leukocyte endothelial reaction, which, in turn, incites an inflammatory response that ultimately destroys the venous valves and weakens the venous wall.[31] The perforating veins most commonly associated with recurrent varicosities are the midthigh perforating vein, the distal thigh perforating vein, the proximal anteromedial calf perforating vein, and the lateral thigh perforating vein, which connects the profunda femoris vein to surface varicosities.

Finally, there is a fifth cause of recurrent varicosities, which is out of control of the operating surgeon—namely, the genetic tendency to form varicosities through development of localized or generalized vein wall weakness, localized blowouts of venous walls, or stretched, elongated, and floppy venous valves.[32]

SAPHENOUS SURGERY

For varicose vein surgery to be successful, two tasks must be accomplished. The first is ablation of reflux from the deep to the superficial veins, including the saphenofemoral junction, the saphenopopliteal junction, and midthigh varices from the Hunterian perforating vein. Accomplishment of this task is guided by the careful preoperative duplex mapping of major superficial venous reflux.

The second task is removal or destruction of all varicosities present at the time of the surgical intervention. Accomplishment of this task is guided by meticulous marking of all varicose vein clusters.

A number of options are available for surgical treatment of varicose veins. Regardless of the specific approach taken, the general technical objectives are the same: 1) ablation of the hydrostatic forces of axial saphenous vein reflux (see Figure 25.3) and 2) removal of the hydrodynamic forces of perforator vein outflow.

Ankle-to-groin stripping of the saphenous vein has been a dominant treatment of varicose veins over the past 100 years.[33,34,35] One argument against routine stripping of the leg (i.e., ankle-to-knee) portion of the saphenous vein is the risk of concomitant saphenous nerve injury.[19] Another argument is that whereas the objective of saphenous vein removal is detachment of perforating veins emanating from the saphenous vein, which are seen in the thigh, the perforating veins in the leg are actually part of the posterior arch vein system

rather than the saphenous vein system. This latter argument notwithstanding, preoperative ultrasonography frequently shows that the leg portion of the saphenous vein is in fact directly connected to perforating veins. Therefore, removal of the saphenous vein from ankle to knee should be a consideration in every surgical case.

OPERATIVE TECHNIQUE

The surgical approach taken must be individually tailored to each patient and each limb. Groin-to-knee stripping of the saphenous vein should be considered in every patient requiring surgical intervention.[36] In nearly all patients, this measure is supplemented by removal of the varicose vein clusters via stab avulsion or some form of sclerotherapy.

Preoperative marking, if correctly performed, will have documented the extent of varicose vein clusters and identified the clinical points where control of varices is required. Incisions can then be planned. As a rule, incisions in the groin and at the ankle should be transverse and should be placed within skin lines. In the groin, an oblique variation of the transverse incision may be appropriate. This incision should be placed high enough to permit identification of the saphenofemoral junction.

Generally, throughout the leg and the thigh, the best cosmetic results are obtained with vertical incisions. Transverse incisions are used only in the region of the knee, and oblique incisions are appropriate over the patella when the incisions are placed in skin lines.

A major cause of discomfort and occasional permanent skin pigmentation is subcutaneous extravasation of blood during and after saphenous vein stripping. Such extravasation can be minimized by applying a hemostatic tourniquet after Esmarch exsanguination of the limb. The pressure in the hemostatic tourniquet should be between 250 and 300 mm Hg, and the tourniquet should not be in place for longer than one hour. If a tourniquet is not used, the entire operation on one limb can be performed with the limb elevated 30º so that the major varicose clusters are higher than the heart. In addition, hemostatic packing can be placed into the saphenous vein tunnel.

The practice of identifying and carefully dividing each of the tributaries to the saphenofemoral junction has been dominant over the past 50 years. The rationale for this practice has been that it would be inadvisable to leave behind a network of interanastomosing inguinal tributaries. Accordingly, special efforts have been made to draw each of the saphenous tributaries into the groin incision so that when they are placed on traction, their primary and even secondary tributaries can be controlled. The importance of these efforts has been underscored by descriptions of residual inguinal networks as an important cause of varicose vein recurrence.[37] Currently, however, this central practice of varicose vein surgery is under challenge, on the grounds that groin dissection can lead to neovascularization and hence to recurrence of varicosities (see Chapter 26).

Preoperative duplex studies have already demonstrated incompetent valves in the saphenous system, and a disposable plastic stripper can be introduced from above downward; alternatively, a metal stripper can be employed.[38] Both of these devices can be used to strip the saphenous vein from groin to knee via the inversion technique. This approach should reduce soft tissue trauma in the thigh.[39]

In the groin, the stripper is inserted proximally into the upper end of the divided internal saphenous vein and passed down the main channel through incompetent valves until it can be felt lying distally approximately 1 cm medial to the medial border of the tibia at a point approximately 4 to 6 cm distal to the level of the tibial tubercle. The saphenous vein is anatomically constant in this location, just as it is in the groin and ankle. If the saphenous vein is removed from the groin to this level, both the midthigh perforating vein, which usually enters the saphenous vein, and the most distal incompetent perforating veins, which are in the distal third of the thigh, will be treated. A small incision is made over the palpable distal end of the stripper. The saphenous vein will subsequently be divided through this incision, and the stripper and the inverted vein will be delivered through it. In exposing the saphenous vein at knee level, the superficial fascia must be incised so as to enter the saphenous compartment. If the stripper passes unimpeded to the ankle, it can be exposed there with an exceedingly small skin incision placed in a carefully chosen skin line. Passage of the stripper from above downward to the ankle serves to confirm the absence of functioning valves, and stripping of the vein from above downward is unlikely to cause nerve damage. At the ankle, the vein should be carefully and cleanly dissected to free it from surrounding nerve fibers. If this is not done, saphenous nerve injury will result, and the patient will experience numbness of the foot below the ankle.

Stripping of the saphenous vein has been shown to produce profound distal venous hypertension. This occurs in virtually every operation, even when the limb is elevated. Therefore, after the stripper is placed, one should consider performing the stab avulsion portion of the procedure before the actual stripping maneuver.

Incisions to remove varicose clusters vary according to the size of the vein, the thickness of the vein wall, and the degree to which the vein is adhering to the perivenous tissues. In general, vertical incisions 1 to 3 mm in length are appropriate, except in areas where skin lines are obviously horizontal. Successive incisions are spaced as widely as possible. Varicosities are exteriorized by means of hooks or forceps. Particularly useful for this purpose are the specially designed vein hooks known by the names Varady dissector, Mueller hook, and Oesch hook.[40] These devices efficiently detach perforating veins from their tributary varicose

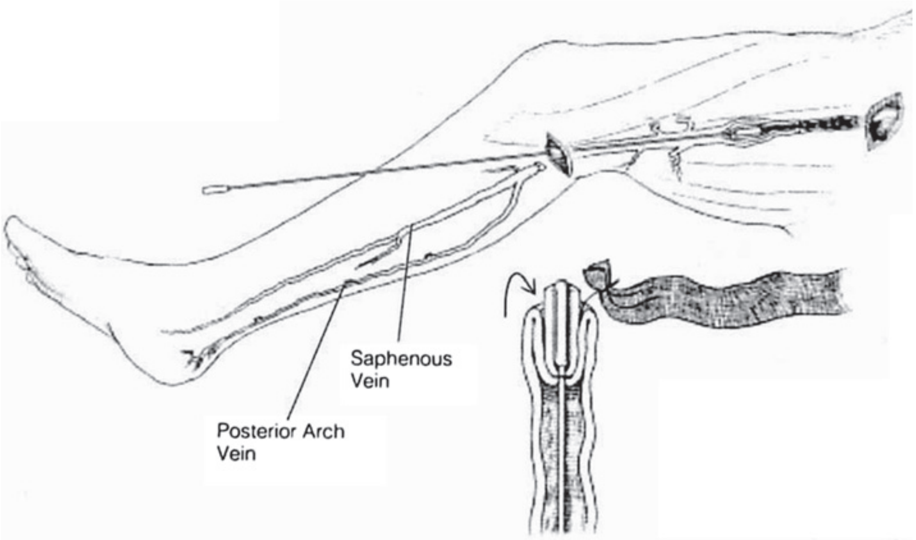

FIGURE 25.4 Adding a hemostatic pack to inversion stripping corrected the principal flaw in inversion stripping, the tearing of the saphenous vein. The pack acted as an obturator, which insured total vein removal. In most instances, the pack entered the vein as it was being removed, thus minimizing the soft tissue trauma.

clusters. Dissection of each perforating vein at the fascial level is not required, and in fact may be cosmetically undesirable. There is no need to ligate or clip the ends of each vein: the combination of leg elevation, trauma-induced venospasm, and direct pressure typically ensures adequate hemostasis. Once exteriorized, the varicosity is divided and avulsed for as long a length as possible. After avulsion, skin edges are approximated with tape or with a single absorbable monofilament suture.

Phlebectomy techniques for varicose clusters have been markedly refined by experienced workers in Europe.[41]

Once the stab avulsion portion of the procedure is complete, the previously placed stripper is pulled distally to remove the saphenous vein. Although plastic disposable vein strippers and their metallic equivalents were designed to be used with various-sized olives to remove the saphenous vein, in fact, a more efficient technique is simply to tie the vein to the stripper below its tip so that the vessel can then be inverted into itself and removed distally.

To decrease oozing into the tract created by stripping, a 5 cm roller gauze soaked in a 1% lidocaine-epinephrine solution is attached to the stripper by using the ligature fastening the saphenous vein to the device (see Figure 25.4). Thus, inversion stripping is accompanied by hemostatic packing. The hemostatic pack, which lies within the saphenous vein, can be pulled into the tract with minimum tissue trauma; when it is not inverted into the vein itself, it can act as an obturator to facilitate removal of the saphenous vein without tearing. As the vein is removed by inversion, the gauze is left in place for hemostasis while the remainder of the surgical procedure is being completed.

Surgical removal of the saphenous vein on an outpatient basis still requires two incisions, one in the groin and the other near the knee. Postoperative compression bandaging is standard, and most patients experience little downtime. Some, however, do experience hematomas, pain, and extensive bruising. Varicosities recur in 15% to 30% of patients treated.[42]

EPILOGUE

Study of surgical saphenous stripping has shown that when undesirable outcomes occur, they become evident quite early. As noted earlier, it has long been accepted practice to dissect tributary vessels at the saphenofemoral junction very carefully, taking each of the vessels back beyond the primary and even the secondary tributaries if possible. In practice, however, such dissection appears to cause neovascularization in the groin. Duplex ultrasound surveillance supports this finding. It has now been amply confirmed that neovascularization causes recurrent varicose veins (see Chapter 26). Clearly, this is a significant disadvantage of standard surgical treatment of varicosities and the alternative techniques of EVLT and VNUS closure© should be considered in every case.

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CHAPTER

26

Neovascularization: An Adverse Response to Proper Groin Dissection

MARIANNE DE MAESENEER

At the beginning of the twenty-first century, surgical treatment of varicose veins continues to be marred by the development of recurrent varicosities. This has always been a very disappointing phenomenon for patients and surgeons alike. Most commonly, recurrent reflux develops in the area of the saphenofemoral junction (SFJ), causing recurrent varicose veins from the thigh downward to the entire leg (see Figure 26.1).[1] Even in clinical centers with a special focus on minimizing recurrence surgeons do not seem to be able to avoid such disfiguring and often disabling recurrent varicose veins.

Some causes of recurrence are obvious: insufficient understanding of venous anatomy and hemodynamics, inadequate preoperative assessment, and incorrect or insufficient surgery (most frequently too superficial ligation of the SFJ). However, recurrence at the SFJ cannot always be explained by technical inadequacy of the original surgical intervention. Its development has also been attributed to *neovascularization* in the granulation tissue around the ligated stump.[2] Neovascularization is defined as new blood vessel formation (= angiogenesis) occurring in abnormal tissue or in an abnormal position. In some instances the growth of new blood vessels from the surrounding tissue may be induced by diffusible chemical factors (angiogenic factors). In the particular context of varicose recurrence after Great Saphenous vein (GSV) surgery, the term neovascularization describes a phenomenon of formation of new venous channels between the saphenous stump on the common femoral vein (CFV) and the residual GSV or its tributaries (see Figure 26.2). Neovascularization is a distinctly uncommon finding when the true SFJ has not been divided. However, when the SFJ has been ligated properly, it is actually a marker of an anatomically correct operation, as well as the best explanation for SFJ reconnections after such an operation.

Many surgeons only start to recognize the phenomenon after having to reoperate on patients with recurrent varicose veins some years after a previous varicose vein operation "correctly" performed by themselves. The observations during reexploration of the groin at the level of the saphenofemoral junction then frequently show neovascularization as the explanation for the recurrence. Despite the fact that this frustrating phenomenon frequently is encountered by each vascular surgeon, its nature and pathophysiology (hence its prevention) are poorly understood and the subjects of intensive ongoing research.

A HISTORICAL PERSPECTIVE

Surgical ligation of the GSV above or below the knee has been practiced for many centuries, starting with Paulus of Aegina in 660 A.D. However it was not until the nineteenth century before the effect of ligation on the vein itself and on the venous hemodynamic situation became better understood.

In 1861, Langenbeck[3] described in detail what exactly happened with a vein after surgical ligation. He noticed that a vein had a very important regeneration capacity and that a new vein channel could be formed after ligation or extirpation of a piece of vein:

> In one case of very large varix of the great saphena in a young man I had extirpated the enlarged vein in the length of three inches and ligated the upper and lower ends. One year later I found, in the region of the scar tissue of the extirpation, a new vein channel of the thickness of the quill of a crow's feather, which again joined the both ends of the fully functioning saphena.

Looking at his detailed description now, one and a half centuries later, this could be considered as the first real

FIGURE 26.1 Prominent recurrent varicose veins with venous ulcer in a 32-year-old man who underwent comprehensive saphenofemoral junction ligation and stripping of the great saphenous vein above the knee 8 years earlier.

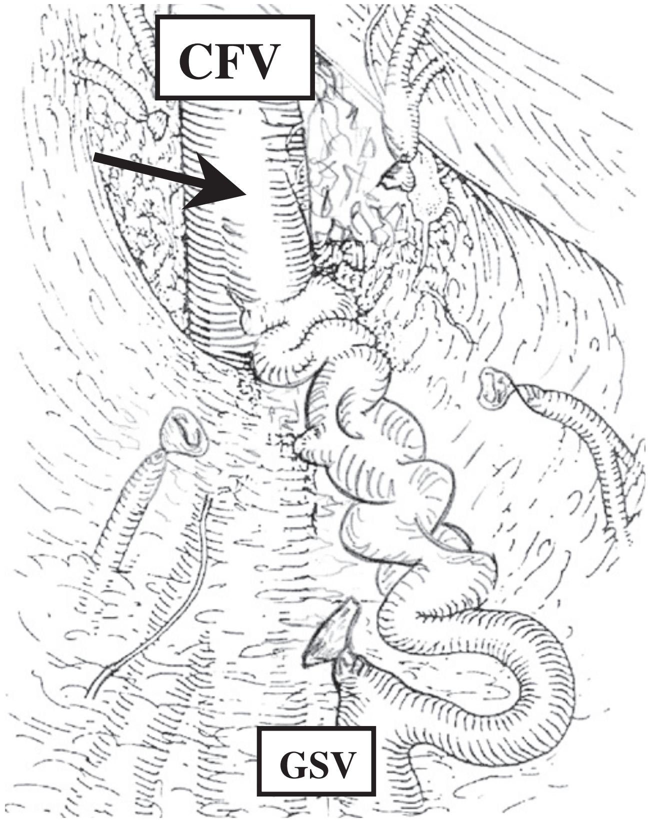

FIGURE 26.2 Diagram of neovascularization in the groin after correct previous ligation of the Great Saphenous vein (GSV) and all tributaries at the saphenofemoral junction, without stripping the GSV. A new vein (arrow) is bulging at the anteromedial side of the common femoral vein (CFV) and continues downward as a very tortuous vein, connecting again with the retained GSV trunk. If the above knee GSV has been stripped, it may connect with any other superficial vein remnant.

description of formation of new veins after ligation (which could possibly lead to recurrence of varicose veins later on).

Throughout the nineteenth century, surgical treatment of varicosity of the GSV was limited to simple ligation and transection at a site in the thigh where there were relatively few tributaries. Therefore it was obvious that, if recurrence occurred, the cause was situated at the site of ligation in the thigh. In the beginning of the twentieth century, Homans[4] introduced saphenofemoral junction ligation in the groin. He advocated ligation of all tributaries to the terminal portion of the saphenous vein to prevent restoration of venous continuity through a collateral network in the groin. From that time, the theory of recurrence through preexisting collateral veins gained ascendancy over the earlier theory of recurrence through growth of new vessels. Ever since, inadequate operation by the previous surgeon was claimed to be the main cause of recurrence. Only a minority believed that recurrence also could occur after accurately performed saphenofemoral ligation through formation of new vessels. In explaining the genesis of this phenomenon, Sheppard[5] hypothesized that, “under the influence of the high femoral pressure, the capillaries and venules in the granulation tissue (of the newly forming scar) developed into dilated tortuous channels.”

Starnes et al.[6] described a radiological type of recurrence of varicose veins, which could occur even after skillful high ligation. He was convinced that ascribing all thigh recurrences to a missed venous branch at the time of high ligation of the saphenofemoral junction was too simple an explanation. In four out of six cases with clinical recurrence varicography demonstrated the presence of a new, tortuous segment of vein at the site of the previous operation. The proximal and distal cut ends of the GSV or one of its branches had been rejoined by new vessels, described as “a zigzag of recurrent vein joining the remnant of the GSV with the femoral vein.”

During the period 1950 to 1980, Glass[7–9] led surgeons to focus again on recurrence of varicose veins after surgery through "regrowth of veins." He published his clinical and experimental work concerning this problem, in 1987 mentioning the term *neovascularization* for the first time.[7] In this study, a series of patients with venous ulceration due to GSV insufficiency were treated in stages. First, a transection of the GSV was performed in the lower part of the thigh and all side branches at that site were ligated. In a second stage, individually timed for each patient by healing of the ulcer, the SFJ was ligated in combination with stripping of the GSV. During the same operation the ends of the vein at the site of the original transection in the lower thigh were excised together with the tissue intervening between them. The excised specimen was examined by injecting normal physiologic solution into the distal segment. Continuity between the proximal and distal cut end had been reestablished through small vessels after 40 weeks and through larger dilated vessels after 64 weeks. The histological examination showed organization of the blood clot starting soon after the operation, with blood vessels moving in from the surrounding tissue. At six weeks, there was recanalization of the thrombus occluding the vein and vessels started to grow from the transected vein end. At 18 weeks it could be observed that new vessels between the cut ends were arranged in a parallel formation. At 40 weeks, continuity of the vein had been completely restored through small vessels, which were continuous with the transected vein ends. The new vessels were very thin-walled with muscular tissue. At the site of the previously closed vein end it seemed to be reopened, establishing a new connection with the surrounding tissue. He hypothesized that one of the important triggers for restoration of continuity was a large pressure difference in a vein proximal and distal to the site of transection.

He also studied the gross anatomy and histology at the level of the SFJ during reexploration of the groin.[8,9] In the majority of limbs a newly formed vessel or complex of vessels was found in connection with the former saphenous stump proximally and with varicose veins on the thigh distally. Macroscopic examination revealed several lumens in an irregular mass of vein tissue and cords or bands traversing the lumen, which suggested that the vessels were newly formed and not preexisting. Large lymph nodes were often in close proximity to them. The histology confirmed the macroscopic findings: an irregular vessel wall with a varying thickness at different points of the circumference, often with several lumens. Also typical was the presence of many small vessels close to the newly formed vessel and in neighboring lymph nodes. These studies clearly indicated that neovascularization had played an important role in recurrent saphenofemoral incompetence after a correctly performed SFJ ligation.

NEOVASCULARIZATION: TODAY'S EVIDENCE

Sonographic Evidence

Duplex scanning can provide the necessary anatomical and functional information about the nature of recurrence and has become the investigation of choice in patients with recurrent varicose veins. Jones et al.[10] found that neovascularization at the SFJ was the most common cause of recurrence in 113 legs two years after stripping of the GSV. Typical serpentine tributaries arising from the ligated SFJ were detected in 52% of limbs. Another duplex-based prospective study revealed some degree of neovascularization in 14% of 177 limbs already at one year after flush saphenofemoral or saphenopopliteal junction ligation.[11] The clinical relevance of finding neovascularization on postoperative duplex ultrasound was examined in a long-term follow-up study at the same institution almost five years (56 months) after the varicose vein operations.[12] In 68% of limbs with clinically obvious recurrent varicose veins, neovascularization (with new veins of >4 mm diameter, pathological reflux, and connected to recurrent varicose veins) was present at the site of the saphenous ligation on duplex examination, whereas in limbs without recurrent varicose veins this degree of neovascularization was seen in only 9% of cases (see Figure 26.3). A reintervention was proposed to all patients with disabling recurrent varicose veins and obvious neovascularization on duplex examination. Fifteen reinterventions were performed. In all 15 reinterventions, newly formed vessels were present exactly at the site of the previous saphenous ligation, which confirmed the duplex findings in all of them. Histological examination of the excised tissue in some of the reoperated cases illustrated the presence of typical tortuous veins (see Figure 26.4). These findings demonstrate the clinical relevance of duplex-detectable neovascularization in the long-term follow-up after varicose vein operations.

Histopathological Evidence

Nyamekye et al.[13] provided further evidence that neovascularization was the cause of recurrence. Histological examination of the venous tissue blocks, excised during groin reexplorations, showed neovascularization in 27 of 28 blocks, characterized by vein tortuosity, small size, and mural asymmetry and lack of intramural nerves on immunohistologically S100 stained sections. The authors drew attention to the fact that a negative demonstration of a focal structure, such as a mural nerve seen on S100 stained sections, is never entirely convincing and that a more useful tool for the diagnosis of neovascularization was not yet available. In spite of this warning, the findings of his study

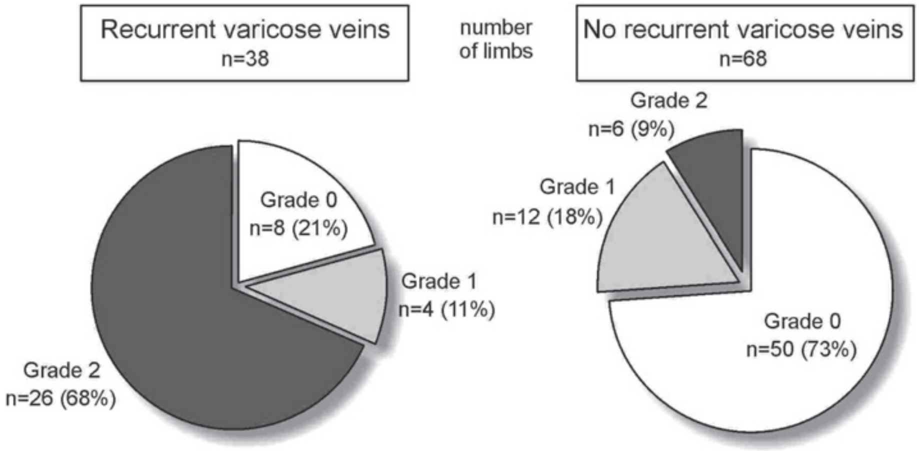

FIGURE 26.3 Proportional incidence of different degrees of neovascularization according to duplex ultrasound scanning of the groin at long-term follow-up in limbs with and without recurrent varicose veins. Grade 0: no neovascularization; Grade 1: tiny new vein <4 mm; Grade 2: tortuous new connecting vein with a diameter ≥4 mm and with pathological reflux.

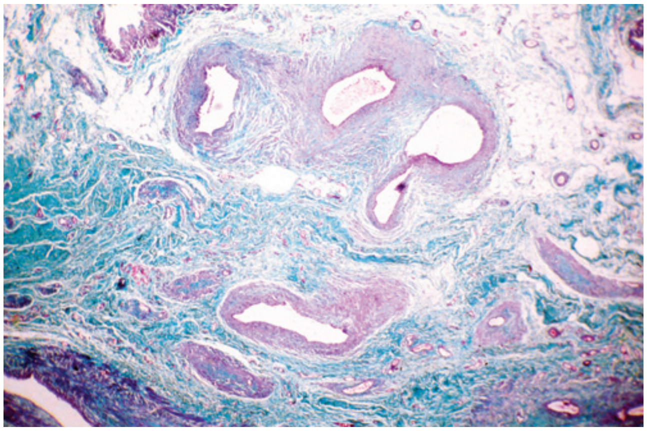

FIGURE 26.4 Histological section of an excised tissue block in the groin showing tortuous newly formed veins within the scar tissue (Masson's trichrome stain, original magnification ×40).

were cited in many instances as the final histological description of neovascularization.

The causality of recurrence was further investigated by van Rij et al.[14] by correlating findings from duplex ultrasound scans before operation with histological findings in specimens taken from the groin at operation and resin casts made from some of the excised tissue blocks (see Figure 26.5). Neovascular channels of variable size, number, and tortuosity accounted for the ultrasound appearances in the vast majority of examined specimens. These new vessels connected to the CFV at the site of the previous SFJ. At

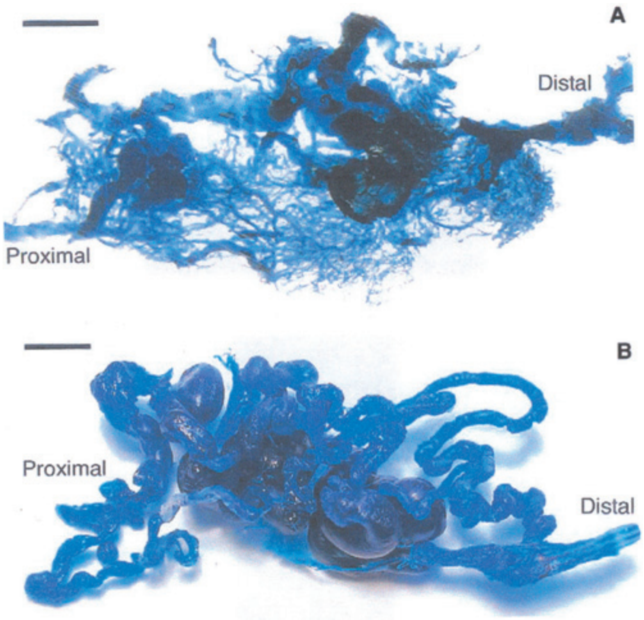

FIGURE 26.5 Vascular casts of recurrent refluxing saphenofemoral junction (SFJ) specimens, showing the connecting network of vessels. In both specimens there are abundant tortuous vessels. Casts injected from the SFJ show resin present in the connecting network of vessels. Notice the variation in size of the abundant tortuous vessels in both specimens. **A**: Though several channels are larger, there are more than 100 channels running in a similar proximal distal direction. **B**: Three large-diameter channels dominate the cast; however, there are also small channels present in continuity. Note the injecting cannula (distal). Scale bars: **A**, 5 mm; **B**, 10 mm. (Reprinted from AM van Rij, GT Jones, GB Hill, P Jiang. Neovascularization and recurrent varicose veins: more histologic and ultrasound evidence, J Vasc Surg. 2004. 40: 296–302, Copyright 2004, with permission from The Society for Vascular Surgery.)

histological examination such neovascular channels were lined by a simple squamous endothelium overlying a medial layer consisting of two to five layers of vascular smooth muscle. They lacked elastic fibers, had no distinct intimal medial boundary, and no distinct adventitia. In both studies,[13,14] the definition of neovascular vessels was based mainly on negative criteria: no intramural nerves, no three-layered wall structure, and lack of lumen regularity. Stücker et al.[15] added a positive criterion that scar tissue must always surround a newly formed vein. In the 91 groins they studied, the apparent cause of recurrence was original misidentification of the true SFJ in 68%, all with a three-layered wall structure and even presence of valves in 18 limbs. Neovascularization was present in only 26% of the examined tissue samples. This endorses reciprocity that exists between neovascularization and anatomical misidentification: the more cases of improper ligation of the SFJ in a particular study group of limbs with groin recurrence, the less cases of neovascularization. When the true SFJ has been missed and a portion of the GSV has been left intact, attached to the CFV, the immediate postoperative hemodynamic situation remains unchanged, with flux and reflux still going freely to and from the saphenous remnant and untouched tributaries. Hence recurrence can start to develop from the moment of operation. In such instance the impetus for postoperative neovascularization beyond basic wound healing is minimal or missing. On the contrary, after correct ligation, the hemodynamic situation at the SFJ changes completely, and other pathophysiologic mechanisms start acting, leading to postoperative formation of neovascular vessels, potentially responsible for later clinically relevant recurrence.

RESEARCH ON THE PATHOPHYSIOLOGY OF SAPHENOFEMORAL RECURRENCE AND THE ROLE OF NEOVASCULARIZATION

The ultimate answer to the question, does neovascularization at the ligated SFJ really exist? still has to be given. Because animals do not suffer from varicose veins, an animal experiment is hardly possible to prove the existence of neovascularization. Therefore it can be proved only in an indirect way. Observations made in patients prospectively studied after varicose vein operations with duplex scan are very useful. Moreover in patients operated upon because of recurrent varicose veins preoperative duplex findings can be compared with visual inspection at the previous ligation site during reexploration and histological examination of the excised tissue blocks from the scar tissue in the groin. Although findings from such studies may be suggestive for neovascularization, none of them is conclusive. This means that further observational studies will not definitely answer this question.

More fundamental research should focus on the potential pathophysiological mechanisms that could explain how new veins can develop after correct SFJ ligation: angiogenic stimulation in the free endothelium of the ligated stump, transnodal lymphovenous connection, dilation of small adventitial vessels in the vasa vasorum of the femoral vein, or disturbed venous drainage of the ligated tributaries of the SFJ. All of these occur on a background of the normal wound-healing process, in which angiogenesis is an important component, potentially giving rise to a more generalized, field-related neovascularization in the groin.

Angiogenic Stimulation in the Free Endothelium of the Saphenous Stump

After surgical ligation and transection of the GSV, angiogenic stimulation in the free endothelium of the ligated stump has been claimed to be one of the most important triggers for the onset of the neovascularization process. Such stump-related neovascularization might originate from hypoxia-induced activation of endothelial cells distal to the stump ligature, which could be mediated by growth factors.[16] Another cause of stump-related neovascularization could be inflammation related to ligature, particularly those of absorbable material, or to the results of dissection in the immediate area. Irrespective of its original impetus, stump-related neovascularization is the mechanism most compatible with the duplex-imaging morphology of recurrent SFJ reflux. It offers a simple, axiomatic solution to reduce the incidence of neovascularization: “no stump, no stump-related neovascularization.”

Transnodal Lymphovenous Connection

Lefebvre-Vilardebo[17] has focused on the important role of the lymph nodes in the neighborhood of the ligated saphenous stump. At postoperative duplex examination of the groin he described the presence of tiny (1 to 4 mm) refluxing veins passing through the surrounding lymph nodes, which could be indicative for possible evolution to recurrent varicose veins. Study of the lymph nodes by means of high definition ultrasound before and after surgery at the SFJ may help to clarify the role of lymph nodes and lymphovenous connections. In previous studies histological examination mainly focused on excised tissue blocks from the scar tissue in the groin at reoperation.[8,13–15] To improve our understanding of the histological alterations in recurrent varicosis, it might be interesting to investigate primary and recurrent varicose veins, normal vessels of the saphenofemoral area, and lymph nodes and lymph vessels of this area, and compare these findings with those at other localizations.

Dilation of Small Adventitial Vessels in the Vasa Vasorum

Theoretically, dilation of small adventitial vessels in the vasa vasorum of the femoral vein could be responsible for new connections between the deep and superficial venous system. Venous endoscopy of the femoral vein, done to assess valve function, occasionally has shown extremely small medial or lateral orifices near the entrance of the GSV. These have been thought to be the openings of tiny tributaries that are too small to show on phlebography or duplex sonography. The observers, for this reason, cannot be certain that these are not just vasa vasorum serving the vein wall and having no external connections, but they have postulated that these tiny orifices might enlarge, to become conduits of blood refluxing to the superficial veins.

Disturbed Venous Drainage of Ligated Tributaries

Disturbed venous drainage of the ligated tributaries of the SFJ has recently been cited as a potential pathophysiological mechanism to explain recurrence in the groin. Chandler et al.[18] have suggested that neovascularization might be driven not only by angiogenic stimuli inherent to the wound healing process, but also by localized venous hypertension, or "frustrated venous drainage" secondary to ligation of tributaries. This tributary ligation might interfere with normal venous drainage of the superficial tissues of the lower abdomen and pudendum. The presence of neovascular cross-groin collaterals (small veins passing from the anterior abdominal wall, across the groin, toward the thigh) in some cases at postoperative duplex examination, or reoperation could be an illustration of this hypothesis. Moreover, the idea that localized venous hypertension might be a trigger for neovascularization is supported by the findings in the recently developed alternative techniques consisting of ablation of the saphenous vein by radiofrequency or laser energy without a groin incision. These procedures were not associated with neovascularization in the groin according to duplex scan follow-up.[19] Opposite to the situation of "frustrated venous drainage" following ligation of tributaries in the groin, leaving open these tributaries could reduce the stimulus to neovascularization as the normal venous drainage of the lower abdominal and pudendal tissues would have been preserved. Further studies will be needed to elucidate this pathophysiological issue.

Constitutional Risk Factors

In addition to all the previously mentioned pathophysiological mechanisms, constitutional risk factors, which potentially could enhance the tendency to recurrence, should also be further examined. The importance of risk factors such as female gender, left-sided disease, associated deep vein incompetence, severe chronic venous disease (C4–6 of the CEAP classification), obesity, subsequent pregnancies after surgery, which all have been claimed to promote recurrence, should be prospectively studied.

EFFORTS TO MITIGATE NEOVASCULARIZATION-RELATED RECURRENT REFLUX

Barrier Techniques to Contain Neovascularization

Containment involves constructing an anatomical barrier or inserting a prosthetic barrier between the ligated SFJ stump and the surrounding superficial veins in the groin. Various barrier techniques recently have been studied in primary as well as in recurrent varicose veins, with different rates of success.[20,21] In particular, in repeat surgery at the SFJ, patch saphenoplasty at the level of the religated saphenous stump significantly improved the clinical and duplex scan results, after a follow-up period of five years.[22]

Endoablation of the GSV Stump

Isolating the stump endothelium from the wound milieu, by oversewing the "mouth" of the ligated SFJ with a running polypropylene suture resulted in reduction of recurrent reflux on color duplex venous imaging two years after operation.[23] Other investigators have chosen to destroy the stump endothelium, with chemical or heat cauterization, or in some instances to reduce the amount exposed by placing a second ligature near the free end of the GSV stump, all without conclusive results.

Abandoning SFJ Ligation?

Finally, what about comprehensive *SFJ ligation*, the "sacred cow"? Although we have always been taught that an accurate groin dissection with detachment of all tributaries is the ideal method to prevent recurrence from the groin, in fact, the reverse could become true during the forthcoming years. The usefulness of stripping the GSV (above knee) rests on firm experimental clinical evidence, but the importance of ligating all tributaries of the GSV in the groin is assumed rather than proved. Chandler et al.[18] attempted to define the role of extended SFJ ligation in a study on endovenous radiofrequency obliteration. Because endovenous obliteration can be done with or without a groin incision or SFJ ligation, they compared no ligation with extended SFJ ligation. The nonligation group, by its nature, coincidentally

embraced the no stump, no stump-related neovascularization axiom. They found no notable between-group differences in 57 limbs at one year. Both groups had less than 10% recurrence of either reflux or varicosities. These results questioned the widely held but unproved axiom that SFJ ligation with ligation of all tributaries is an essential component of the treatment of GSV insufficiency. Maybe complete removal of the thigh portion of the GSV could be sufficient to achieve equal therapeutic benefits. The quite revolutionary idea of abandoning SFJ ligation in the management of primary varicose veins associated with GSV reflux will not be widely accepted without a prospective, five-year, randomized study.

Alternative Treatment Methods without SFJ Ligation

Endovenous treatment methods do not seem to be associated with neovascularization in the groin and could therefore become the future method of choice for treatment of primary varicose veins. The results of GSV radiofrequency obliteration after two and three years are promising, and duplex ultrasound findings confirm the absence of neovascular veins in the groin.[19] Endovenous laser treatment is another technique developed to treat saphenous vein incompetence. If duplex scan showed occlusion of the vein one year after the procedure, it remained occluded at further controls up to three years after treatment.[24] Ultrasound-guided foam sclerotherapy was introduced as a third alternative treatment method. The increased efficacy of foam, compared to liquid sclerotherapy, enabled treatment of varicose veins with larger diameter and even main superficial trunks. Encouraging results have even been obtained even in patients with recurrent varicose veins.

The results of these alternative treatment methods are promising, but yet inconclusive. Follow-up periods of at least five years are needed to better evaluate whether the recurrence rate after primary or recurrent varicose vein treatment could be reduced with these procedures.

Importance of Follow-up after Treatment

Whatever technique has been used, serial duplex examinations remain the cornerstone of follow-up. Early evaluation, two to three months after the procedure, is useful for initial quality control of the completeness of the (surgical) intervention. Further controls may help to understand and define the process and causes of recurrence. It has been shown that color duplex scan of the SFJ one year after GSV surgery has a high sensitivity and specificity. It accurately predicts which patients are more likely to have a good outcome five years after surgery.[25]

CONCLUSION

After proper groin dissection, neovascularization is both a marker of thoroughly performed SFJ tributary ligation and a pathway for superficial to deep reconnections. It is remarkably focused on the site of the former SFJ and it appears to arise because of stimuli that are related to healing of the surgical wound as well as to the continued presence of diseased superficial vein remnants.

Duplex scanning has rationalized the surgical management of lower extremity venous disease. Thorough preoperative assessment with duplex ultrasound, in particular of the groin, now leads to a well-established surgical approach, guided by the venous anatomy of each individual patient, and optionally a less invasive endovascular approach. Duplex scanning also offers a unique opportunity to compare the post-treatment events of these two approaches with early and serial post-treatment scanning. In this process, the surgeon will have an opportunity to assess his or her own technique and to uncover variables that might be associated with relative stability or progression to clinically relevant reconnections and new varicosities. The ultimate truth will come from knowledge of cell signalling and other molecular events that would require repeated tissue sampling, timed in accord with the evolving duplex anatomy.

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C H A P T E R

27

Principles of Ambulatory Phlebectomy

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Ambulatory phlebectomy (AP) is a surgical procedure designed to allow outpatient removal of bulging varicose veins. This treatment originally was described and performed by Aulus Cornelius Celsus (56 BC–30 AD) in ancient Rome.[1] However, the art of AP was revived, redefined, and practiced by the sagacious Swiss dermatologist Robert Muller in 1956. Prior to Muller's reintroduction of AP, veins were removed with relatively large incisions and ligation of venous ends. Muller developed the stab avulsion method that is now in widespread use. Characteristics of Muller's AP technique are absence of venous ligatures, exclusive use of local infiltration anesthesia, immediate ambulation after surgery, 2-mm incisions, absence of skin sutures, and a postoperative compression bandage kept in place for two days, then replaced with daytime compression stockings for three weeks.

It is of interest that after its introduction, the medical–scientific community exhibited minimal interest in Muller's AP procedure. Muller published his first manuscript on AP in 1966;[2] however, AP did not gain popularity in the United States until the American surgeon Gabriel Goren published his findings in 1991.[3] In contemporary vein centers, AP is a common office-based procedure performed with local anesthesia. Unless the patient's history suggests other comorbidities, hematologic or other laboratory investigations are not generally required.

INDICATIONS

AP is indicated for the removal of varicose venous tributaries, when visible and palpable on the surface of the skin. AP is simple to perform, is well tolerated, and can be used in conjunction with other treatment modalities. The most important concept for the practitioner treating varicose veins to understand is that simple vein removal, without proper diagnostic evaluation, will not yield good results. It is critical to recognize that bulging veins usually are associated with an underlying source of venous hypertension, and treatment of the source is as important as the vein removal itself. Prior to performing AP the treating physician must perform a thorough evaluation with duplex ultrasound imaging to identify the source of venous hypertension and its most proximal point of reflux. To prevent recurrence, the refluxing source in continuity with the varicose veins should be eliminated prior to undergoing AP.

The most common source of ambulatory venous hypertension is an incompetent superficial system, usually the Great Saphenous vein (GSV). An incompetent GSV, in continuity with a bulging venous tributary, commonly is encountered in patients presenting with venous disease. However, venous hypertension also may originate from deep veins, perforating veins, or any combination of superficial, perforating, and deep systems. If a source of ambulatory venous hypertension is identified during the preoperative studies, it should be treated either prior to or at the same time as AP. There are many techniques available to treat axial or perforator vein incompetence that are beyond the scope of this essay. Briefly, superficial axial vein reflux may be corrected by surgical, thermal, or chemical means.

PREOPERATIVE MAPPING

Mapping is done prior to commencing AP and is a critical step in the procedure. It must be comprehensive. The key to success is accurate marking of the surface bulges with an indelible marker in the standing position (see Figure 27.1).

FIGURE 27.1 Mapping.

Marking is performed in the standing position because hydrostatic pressure is no longer active when the patient is supine. Stated differently, bulging veins disappear when patients lie flat because the local venous pressure decreases to near zero mmHg. We prefer mapping these veins using visual inspection and palpation; other investigators prefer transillumination mapping.[4] Precise mapping provides a blueprint for the operator to locate veins with ease, careless mapping provides a poor blueprint and results in suboptimal surgical results. Patients should avoid placing moisturizing lotions on their legs the morning before surgery as this promotes smudging during the preoperative surgical scrubbing process, thereby undermining the quality of the blueprint.

ANESTHESIA

Tumescent anesthesia provides a safe, easy to administer, and comfortable anesthetic technique for use with ambulatory phlebectomy. The technique of tumescent anesthesia involves infiltration of the subcutaneous compartment with relatively large volumes of a dilute mixture of a buffered local anesthetic solution. Preparation of the tumescent solution is easily accomplished. Our preparation requires a 50 cc vial of 1% lidocaine with added 1 : 100,000 mg of epinephrine mixed with 500 cc of Ringer's lactate. This gives a 0.1% preparation of lidocaine with epinephrine, which is delivered with a 30 cc syringe and 20-gauge needle subdermally, under pressure, until the characteristic peau d'orange effect is seen on the skin.

This form of anesthesia requires no specialized training or expensive equipment and offers several intraoperative as well as postoperative advantages not found in traditional local anesthesia. Not only is excellent anesthesia provided to relatively large areas of the leg, but the tumescent fluid hydrodissects the subcutaneous fat. It enters perivenous tissues under pressure, thus facilitating vein extraction. This has led to use of this technique not only in AP, but also in surgical stripping[5] and thermal ablation of the Great Saphenous vein.

Originally developed by Klein[6] in 1987 for use in liposuction, Cohn[7] in 1995 introduced the technique of tumescent anesthesia for use in ambulatory phlebectomy. Surprisingly, as the concentration of lidocaine was lowered during the developmental stages of the technique, it was observed that the anesthetic effect was augmented until a threshold 0.04% was reached. Klein has shown through clinical studies involving assays of lidocaine in peripheral blood, that doses well above the manufacturer's recommendation are safe. The widely held dogma that lidocaine administration should be limited to 7 mg/kg was based on extrapolated data from procainamide levels. This dogma was rigidly adhered to from 1948 because of recommendations from the manufacturer. It is now known through Klein's work that a dose of 35 mg/kg of dilute lidocaine solution is well tolerated.[8] Further documentation and years of safe use have made it the standard for anesthesia in liposuction surgery. However, the authors have found that exceeding 7 mg/kg is rarely necessary to complete a unilateral lower extremity endovenous thermal ablation with concomitant AP.

Infiltrating solutions should contain epinephrine in appropriate concentrations to reduce the incidence of hematoma and induce a more gradual absorption of lidocaine into the bloodstream. When general anesthesia is used for this surgery (i.e., dry technique), there is no infiltration of local anesthetic or vasoconstrictor agents. This results in blood loss and significant pain. Other advantages of tumescent anesthesia include the ability to anesthetize large areas of the body without toxicity, positive effect on intravascular fluid status, avoidance of general anesthesia, less pain, and shorter postoperative recovery time.[8]

Infections are rare after liposuction and AP with tumescent anesthesia, and usually are confined to an incision site.[9] Infections have not been seen in our practice since we began office-based AP surgery with tumescent anesthesia. The reason for the low rate of infection is not clear, although there are reports of lidocaine concentration-dependent

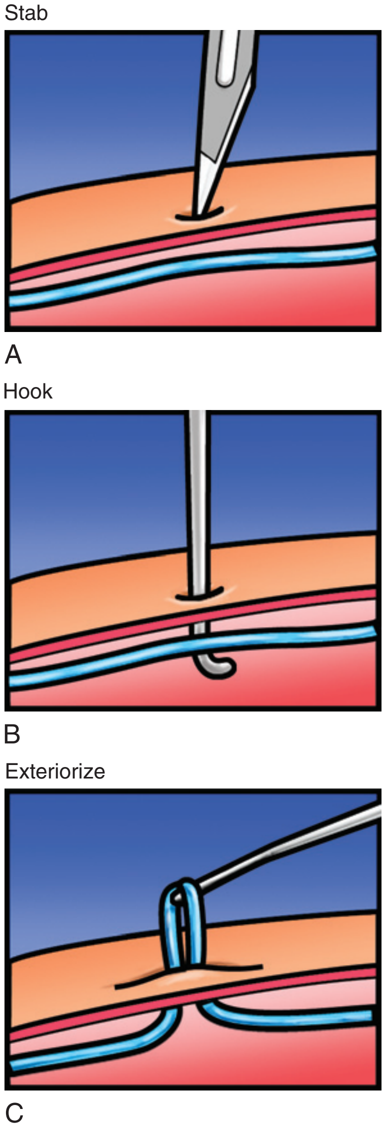

FIGURE 27.2 Stab incisions.

bacteriostatic and bactericidal activity. Pathogens commonly found on the skin may be sensitive to this activity.[10]

SURGICAL TECHNIQUE

Incisions

Access to varicose veins is accomplished with a sharp instrument using small stab incisions (see Figure 27.2). Incisions of 1–3 mm in length are usually sufficient to extirpate even the largest veins. The methods and required tools are simple and basic. The most popular instruments for creating incisions are No. 11 scalpel blades, 18-gauge needles, and 15-degree ophthalmologic Beaver blades. Incision length should correspond to vein size, but are rarely larger than 3 mm. Small varicose veins are extracted through an 18 gauge needle puncture, and larger veins are removed through 2 mm incisions made with an No. 11 scalpel blade. The incisions are oriented vertically on most areas of the lower extremity. Horizontal incisions are preferred around the knees and ankles.

Widening of incisions with a hemostat should be avoided because this results in an increased potential for unsightly scars and/or wound infections. If wound margins are traumatized this may lead to increased pigmentation in the postoperative scar. There have been anecdotal reports of “tattooing” the skin when the incision is placed through the indelible ink mark made during the preoperative mapping process. This has not been the experience of the authors.

Reimbursement for AP has been established with Current Procedural Terminology (CPT) codes. Insurance carriers base the remuneration for services on the number of stab incisions; therefore, it is important to count the total number of incisions made during each case and document this information in the clinical record.

Hooking and Extraction of Vein

Hooking the target vein through the small incision is the next step (see Figure 27.2). There are many instruments available on the market to accomplish this goal, ranging from inexpensive to very expensive. Most operators use hooks to elevate the vein from the wound whereas others reach into the wound and grasp the vein with fine hemostats. The most popular hooks are medical grade with the developer’s name used for identification (i.e., Muller, Oesch, Tretbar, Ramelet, Verady, and Dortu-Mortimbeau). However, we prefer hooks manufactured for crocheting; they are readily available, come in a variety of sizes, and are suitable for autoclave sterilization between uses.

Using a hook of choice, the vein is exteriorized from the wound (see Figure 27.2). Hooks need not be introduced into the wound deeper than 2–3 mm and should be inserted gently and deliberately to avoid unnecessary trauma to the wound margins. Gentle probing and “searching” for the target vein with the hook are routinely necessary and should be done with great care. Once a segment of vein is exteriorized from the wound it is extracted. The vein is grasped with fine hemostatic clamps, and using gentle traction in a circular motion the vein is teased out of the wound. Dissection of the vein from its perivenous investments greatly facilitates its extraction. Perivenous tissue issuing from the wound is excised at the skin level. This tissue should never be forcefully pulled out of the wound. Care should be taken during extraction not to enlarge the wound, especially in the elderly.

When traction is applied to the vein, the skin adjacent to the wound will momentarily depress downward. Attention to this detail gives the operator an idea of where to place the

FIGURE 27.3 Vein of Michaelangelo extracted via one 2-mm incision.

Avulsion of venous segments treated by AP is not associated with significant bleeding when tumescent anesthesia is used. Hemostasis is achieved with gentle pressure over the incision site. The epinephrine in the anesthetic solution, enhances the hemostasis process. When extracting larger veins with the stab-avulsion technique, significant force may be required and some minor bleeding may be encountered. Using digital pressure over the wound with a gloved finger generally controls bleeding. Placing the patient in the Trendelenburg position may also augment hemostasis.

Varicose veins are sometimes outflow tracts for perforating veins; therefore, avulsion of varicose veins can disconnect underlying perforators. A perforator may be recognized by its perpendicular course and by the fact that the patient reports discomfort or pain upon traction of the perforator. The perforator is pulled until it yields, and then avulsed. Bleeding is controlled with digital compression. However, in areas difficult to compress (i.e., thigh) or when perforators are very large, ligation is preferred.[11]

next incision. The depression represents the point at which the vein will avulse. The next incision is made near the area of depressed skin and the process is repeated sequentially until all the venous bulges have been addressed. Although all bulges should be marked during the mapping procedure, not all the marks need to be incised if the operator takes care in identifying the skin depressions described earlier. In some cases, segments as large as 12 inches may be removed from a single site (see Figure 27.3). Segmental extraction of very small portions of varicose veins can make the operation quite tedious; in some cases this cannot be avoided.

If vein exteriorization proves difficult, it is better to make larger incisions rather than traumatize the wound's edges since this may cause visible scars. In order to reduce the number of incisions, the incisions are made one at a time. If avulsion proves difficult and the vein breaks, it is more convenient to make more incisions than to increase effort and in return lose time.[11] One should also keep in mind that the skin in elderly patients is thin and easily damaged if not handled properly. This is especially true in the ankle, foot, and popliteal areas.[12]

Several areas of the lower extremity are more challenging when attempting to hook a vein. Areas of previous surgery and the anterior aspect of the knee have thick skin and fibrous underlying tissue, which can make the hooking process difficult. There is a paucity of subcutaneous fat in the pretibial areas and dorsum of the foot that can also prove challenging. With experience one learns to distinguish between the vein wall, which is elastic, and the connective perivenous tissue, which is not. Ultrasound-guided vein hooking is useful for deeper or more difficult veins. AP is not the best technique for removal of the GSV or SSV; we prefer endovenous thermal ablation for these veins.

Incision Closure

The wounds may be left open, or closed with simple sutures or adhesive tape. Whether to close or not close wounds is a matter of judgment. Most operators leave the wounds open and allow spontaneous healing. This technique results in little or no scarring and also has the advantage of allowing drainage of blood and anesthetic fluid into the overlying compressive dressing. A single suture to close wounds near the foot and ankle may be required because of the elevated venous pressure in the upright position in these locations. Frequent post-procedural ambulation will aid in decreasing ambulatory venous pressure in these dependent locations. Adhesive tapes are associated with a high incidence of skin blistering; therefore, these must be used with caution.

Compression Bandage

Careful application of the postoperative dressing cannot be overstated. Careless dressing placement can lead to hematomas, blisters, nerve injury, ischemia, and bleeding. The limb is wrapped circumferentially from foot to groin with a compression dressing and removed after 48 hours. The dressing should be applied with graduated pressure; the amount of pressure should decrease as one proceeds from foot to groin. During placement of the compressive bandage, it is important to pad the lateral fibular head to avoid pressure-induced injury to the deep and superficial peroneal nerves which can lead to footdrop. Patients are encouraged to ambulate immediately after the procedure to minimize thromboembolic complications.

Application of a compressive dressing in obese patients is especially critical because the dressing has a tendency to

unravel. There is a tendency to apply this dressing tightly, but this can lead to undue pressure, blistering, and/or skin necrosis.

POST-PROCEDURE ISSUES

The patients ambulate from the office with a three-layer compression bandage after 10 minutes of post-operative observation. Very little post-operative discomfort is the norm, and is usually easily managed with nonsteroidal anti-inflammatory agents. When the bandage is removed in the office on post-operative day 2, some minor leakage of blood and tumescent anesthesia may be seen in cases where the wounds are left open. These areas are covered with small bandages until dry. We perform a duplex ultrasound at the post-operative visit to exclude the presence of deep vein thrombosis.

Some ecchymosis is to be expected, rarely resulting in permanent discoloration of the skin. Indurated areas are commonly seen and usually decompress without incident over a period of weeks. Firm subcutaneous inflammatory nodules can form directly under the incision, and these, too, are self-limiting. We give the patient three days of postoperative antibiotic prophylactic therapy. After the compression bandage is removed on post-operative day 2, we have the patients wear graduated compression stockings (20–30 mmHg) for two weeks during the daytime.

COMPLICATIONS

Complications from AP in experienced hands are rare and, when they do occur, are minor.[12] The Miami Vein Center to date has performed more than 1500 AP procedures in the office environment. Complications have been limited to hyperpigmentation, telangiectatic matting, seroma, transient paresthesia, superficial phlebitis, blistering, and "missed veins" requiring repeat treatment. Each of these complications occurred in less than 0.5% of cases.

A multicenter study performed in France evaluated 36,000 phlebectomies. The most frequently encountered complications were telangiectasias (1.5%), blister formation (1%), phlebitis (0.05%), hyperpigmentation (0.03%), post-operative bleeding (0.03%), temporary nerve damage (0.05%), and permanent nerve damage (0.02%).[13]

STAGING OF SURGERY

Prior to the advent of endovenous ablation, high ligation and stripping of the GSV usually relegated venous surgery to the operating room. However, with the development of minimally invasive, catheter-based interventions, venous surgery is a simple office procedure.

Complete surgical removal of varicose veins may be achieved in a single session or in separate sessions. Endovenous ablation and AP are suitable for the office, and in the author's practice, routinely are performed together. The advantage of this combination technique is that patients can expect all varicose veins to disappear after a one-hour procedure.

We feel that in order to become a complete vein surgeon, the individual must become facile with all of the available tools. The operator should enter the procedure room with a complete plan of action. The duplex ultrasound device must be an extension of the surgeon's eyes. Duplex ultrasound is essential for managing the patient preoperatively, intraoperatively, and postoperatively. Combining endovenous thermal ablation, AP, and sclerotherapy techniques with accurate imaging will allow the development of a complete treatment algorithm.

We do not look at AP as a solitary procedure, but as part of the armada in the treatment of venous disease. We usually perform endovenous thermal ablation of the saphenous trunk at the same setting as AP because bulging varicose veins are usually in continuity with a refluxing axial vein such as the GSV. Sclerotherapy is also often used simultaneously with AP when the refluxing axial vein is tortuous. This is often the case when the anterior accessory saphenous vein is incompetent or when we treat recurrent varicose veins after previous high ligation and stripping. We try to keep the sites of AP remote from the sites of sclerotherapy for fear of extravasation of sclerosant from fractured vein ends into the subcutaneous tissues. All procedures are guided with duplex ultrasound to get a "roadmap underneath the skin."

Varicosities in continuity with a refluxing truncal vein (e.g., the GSV), and not in continuity with any perforating veins, will diminish in size after endovenous ablation. Therefore, some patients will not require further treatment. However, in review of our last 1000 cases of endovenous thermal ablation of the saphenous vein, AP was performed concomitantly in 86% of cases.

Some operators delay AP until four weeks following endovenous ablation. The argument for this strategy is to allow the bed of varicosities distal to a refluxing axial vein to shrink in size and number. Then, fewer incisions will be required for vein removal at the time of AP.

If the patient returns in the post-operative period and points out veins that were missed during AP, a redo procedure generally is not required. Sclerotherapy, with or without ultrasound guidance, can be performed four to six weeks post-operatively to remove any missed veins. As a general rule, we prefer not to combine AP with ultrasound-guided sclerotherapy of varicose veins, unless the sites are distant from one another. As stated earlier, leakage of sclerosant from fractured vein ends is undesirable. If redo

phlebectomy is required, we allow three months to elapse; this allows the inflammatory response to improve at the original AP sites.

AVOIDING NONTARGET TISSUES

If the treating physician heeds several important suggestions, complications will rarely be encountered. The venous surgeon must have a thorough command of neurovascular anatomy to avoid injury to nontarget tissues such as arteries and nerves. Knowledge of the course of the common femoral artery, superficial femoral artery, popliteal artery, and anterior and posterior tibial arteries will keep the surgeon from injuring these structures while probing to exteriorize a varicose vein. It would be very difficult, although not impossible, to injure the profunda femoris or peroneal arteries during AP. As stated earlier, the hook rarely needs to plunge deeper than 3 mm to contact the target vein.

The saphenous and sural nerves are particularly prone to injury below the knee because of their proximity to the Great and Small Saphenous veins. If the saphenous or sural nerves are displaced by the hook, the patient usually will complain of shooting pain into the foot. This is a sign for the surgeon to gently release the structure and replace it *in situ*. The femoral, obturator, sciatic, tibial, and peroneal (common, deep, and superficial) nerves are deep and generally not disturbed in the hands of a competent surgeon. However, when placing the post-operative compression bandage, the deep peroneal nerve can be injured if the lateral fibular head is not properly padded. Occasionally, hair-sized sensory cutaneous nerves are encountered and inadvertently extracted during the course of AP. They are recognized as small threads and the patient will feel acute sharp pain. The pain usually dissipates after two to five minutes without treatment. If this occurs in the ankle and foot area, chances are that the patient will develop postoperative paraesthesias or areas of dysesthesia that in most cases will be temporary.[14]

TREATMENT OF VARICOSE VEINS FROM NONSAPHENOUS ORIGINS

Bulging varicose veins on the surface of the skin can originate from different sources. Identification of these sources is important because this influences the treatment plan. Varicosities on the medial aspect of the thigh and calf are usually the result of GSV incompetence. In order to minimize the chance for recurrence, the GSV must be eliminated from the circulation. This concept has been substantiated in several prospective randomized clinical trials involving patients who were treated with or without saphenectomy by conventional vein stripping.[15–18] The recurrence rates for limbs without saphenctomy were much higher than those with saphenectomy. Of course, now thermal ablation techniques with either radiofrequency or laser have proven to be the method of choice for eliminating the GSV from the circulation.[19,20]

Varicosities on the anterior thigh usually result from Anterior Accessory Saphenous Vein (AASV) incompetence. These veins usually course over the knee and into the lower leg. Small Saphenous vein (SSV) reflux produces varicosities on the posterior calf. When also present on the posterior thigh, the surgeon must consider a cranial extension of the SSV, which can be identified with duplex ultrasound imaging. Cranial extensions may enter the GSV (Giacomini vein) or enter the femoral vein directly.

In cases where no "feeding source" is found, phlebectomy of the varicosities may be all that is required. Labropoulos[21] has shown that varicose veins may result from a primary vein wall defect and that reflux may be confined to superficial tributaries throughout the lower limb. Without great and small saphenous trunk incompetence, perforator and deep-vein incompetence, or proximal obstruction, his data suggest that reflux can develop in any vein without an apparent feeding source. This is often the case when bulging reticular veins are seen along the course of the lateral leg. This lateral subdermic complex and its vein of Albanese are often dilated and bulging in elderly patients. The underlying source of venous hypertension is usually perigeniculate perforating veins, not easily identifiable with duplex imaging. AP using an 18-gauge needle stab incision and a small crochet hook for exteriorization of the vein is an excellent procedure for this clinical problem. Perforating veins of the thigh or calf also may become incompetent and be sources of ambulatory venous hypertension. These can be treated by a variety of techniques including ligation, subfascial endoscopic perforator surgery (SEPS), and ultrasound-guided sclerotherapy (UGS).

AP VERSUS POWERED PHLEBECTOMY

In a published prospective comparative randomized trial comparing AP with the new technique of transillumination-powered phlebectomy (TriVex), there was no difference in operating time. Although an incision ratio of 7 : 1 favored TriVex, there was no perceived cosmetic benefit among the patient groups. There was a higher number of recurrences in the TriVex group (21.2%; 7 of 33) compared with the AP group (6.2%; 2 of 32) at 52 weeks postoperatively. Assessment of pain scores showed no difference between groups.[22] These findings have been supported by other investigators.[23–27]

It is important to point out that all Trivex procedures were performed in the hospital under general anesthesia, and the cost of disposable equipment used for the TriVex procedure was to $314 per patient. Because the trend for venous surgery is office-based, with local anesthesia, TriVex will likely fall

into disfavor in the future if modifications for office use are ignored.

AP VERSUS COMPRESSION SCLEROTHERAPY

The combination of compression therapy with intravenous injection of a sclerosing agent for the treatment of varicose veins was introduced in 1953.[28] Early studies indicated compression sclerotherapy (Sclero) would be an efficient addition to varicose vein surgery practiced at that time. Although ambulatory phlebectomy was "invented" around the same period,[2] this technique required considerable time to become well-established worldwide. There is one randomized controlled trial on recurrence rates and other complications after Sclero and AP. A total of 98 operations were randomized to either AP (n = 49) or Sclero (n = 49) in a total of 82 lateral accessory varicose veins (LAVs). In this study, polidocanol was used in a 3% solution (Aethoxysclerol; Kreussler & Co., Wiesbaden, Germany), which is equivalent to 1.5% sodium tetradecyl sulfate. One year after Sclero, 12 LAVs had recurred (25%), and only one postphlebectomy LAV (2.1%). After two years, the difference in recurrence was even larger because another six recurrences developed, making a total of 18 recurrences in the Sclero group (37.5%) and only one recurrence in the AP group (2.1%). The authors of the study concluded that AP is the treatment of choice for LAV.[29]

AP FOR OTHER AREAS OF THE BODY

Foot

In recent years there have been several publications on the use of AP for the treatment of varicose veins of the foot and ankle region.[30–32] There are patients who present with serious phlebologic complaints of varicosities of the foot and ankle region that can be alleviated through simple treatment. The venous anatomy of the foot with many parallel veins is complicated; however, safe treatment is possible.

The skin of the foot is thin and fibrotic. Further, there is minimal subcutaneous fat, less protection against trauma of the skin, and important underlying tissues such as tendons, tendon sheaths, and joints. There are more small nerve branches that can be damaged by the hook. As in the popliteal space, there is greater risk of injuring an artery. Moreover, it is possible to grasp and avulse a tendon.

Eyelid

Many ophthalmic plastic surgeons and dermatologic surgeons experienced in sclerotherapy avoid the use of this agent near the eye or use it in substantially lower concentrations and volumes. This is due to fear that the solution may travel to unintended areas of venous circulation such as the central retinal vein, choroidal vortex veins, or even the cavernous sinus via valveless anastomoses.[33] Blindness has been reported following STS injection into a venous malformation partially located in the orbit.[34]

Ambulatory phlebectomy of the periocular vein avoids the concerns regarding thrombotic phenomena within ocular, orbital, or cerebral veins possibly associated with periocular vein sclerotherapy. Weiss[35] reported excellent results on 10 patients who underwent removal of periocular reticular blue veins by AP. A single puncture with an 18-gauge needle sufficed in most cases. It is important to attempt to remove the entire segment, as partial resection may lead to recurrence. The use of postoperative compression for 10 minutes reduces the incidence of bruising. The puncture sites typically disappear quickly without leaving scars.

Hands

In general, inquiries about hand vein treatment come from elderly women who find them unsightly. Often, they have had prior facelift surgery and worry that their hands need rejuvenation to complement the face. Our initial consultation stresses the importance of hand veins for reasons of intravenous access, furthermore, removal of these veins may require central venous access should the patient be hospitalized in the future. If attempts to dissuade the patient fail, we recommend AP as the procedure of choice for hand vein removal. It is performed identical to leg vein treatment, and closely resembles treating the dorsum of foot because of the thin skin overlying the area. Results have been excellent.

OFFICE-BASED AP WITH TUMESCENT ANESTHESIA

Although there are reports of death and serious complications with tumescent anesthesia, these have largely been found in the plastic surgery literature.[36] Complications are described when tumescent anesthesia is used in conjunction with intravenous sedation, and/or general anesthesia.[37] Coldiron et al. recently studied State of Florida data over a four-year period to help clarify actual adverse events occurring in the office setting. There were 77 events reported to the Florida Agency for Health Care Administration (ACHA) from March 1, 2000, to March 1, 2004. Liposuction performed under general anesthesia was the most frequent procedure reported. Five reported deaths and 14 transfer incidents occurred as a complication of liposuction (with or without another associated procedure) under general anesthesia or deep sedation. According to the Florida data, there

Before After

A B

FIGURE 27.4 Before and after photos.

were no problems associated with liposuction using dilute or tumescent anesthesia.[38] Similarly, a malpractice claims study by Coleman and colleagues study supported the safety of office-based liposuction performed by dermatologists using tumescent anesthesia for small-volume fat removal.[39] In addition, Housman and colleagues surveyed 261 dermatologic surgeons performing a total of 66,570 liposuction procedures and found a low rate of serious adverse events (0.68 per 1000) and no reports of associated deaths.[40] All three studies support the safety of tumescent liposuction performed by dermatologists in an office setting.

Because the tumescent anesthetic technique for venous procedures has been adopted from the liposuction community, we feel these data are relevant to subcutaneous venous surgery using dilute tumescent anesthesia. There have been no adverse events reported to the Florida ACHA as a result of varicose vein surgery using tumescent anesthesia.

Advantages of office-based surgery are ease of scheduling for doctor and patient, less paper work (unnecessary duplication of information and record keeping), no waiting for other surgeons to finish their operations, elimination of travel time, and cost containment for the health care system. Furthermore, a staff that performs the same procedures daily is more streamlined and safe.

CONCLUSION

Ambulatory phlebectomy is elegant by its mere simplicity. It is effective and safe with acceptable cosmetic results (see Figure 27.4). AP is a perfect complement to endovenous thermal ablation of the saphenous veins. With this combination, patients can expect all varicose veins to vanish following a one-hour procedure that employed only local anesthesia, in the comfort of a physician's office.

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CHAPTER

28

Powered Phlebectomy in Surgery of Varicose Veins

STEVE ELIAS

PREMISE

The generic name of the TriVex technique is transilluminated powered phlebectomy (TIPP). TriVex is a mechanical method used to remove tributary varicose veins that normally would be excised with the traditional techniques of stab avulsion and hook phlebectomy. The indications for TriVex are the same as for the use of traditional procedures.

INSTRUMENTATION

The TriVex system consists of a transilluminator/irrigator (see Figure 28.1) and a powered resector (see Figure 28.2). The transilluminator/irrigator is placed subcutaneously to provide for visualization of the varicose veins and instillation of the tumescent fluid (see Figure 28.3). Utilizing the powered resector with its rotating blade on suction mode, the varicosities are removed (see Figure 28.4). TriVex has been described as "liposuction of the veins." The resector is a modification of an arthroscopic shaver. The complete up-to-date step-by-step technique will be described later, in a subsequent section of this chapter.

The advantages of the TriVex technique compared to traditional open surgery are speed, efficiency, decreased number of incisions, and more complete removal due to direct visualization of the target veins. Fewer residual and recurrent varicosities are also a theoretical possibility, again, due to a more complete removal of the primary targets. These are presumptive advantages and, in fact, most have been realized.

THE BEGINNING

The TriVex system was developed in 1996 by Greg Spitz, MD, a surgeon from Aurora, Illinois. He was looking for a faster, more efficient way to remove varicose veins. It was a Friday afternoon and Greg was on his third or fourth extensive bilateral vein case. He asked the scrub nurse if there was anything available to more quickly excise the varicose veins. Together they decided to try a small arthroscopic shaver used to treat carpal tunnel syndrome. This seemed to work. Later on, specific instrumentation to allow visualization and transillumination with a modified cystoscope was developed.

After a series of modifications and the addition of tumescent anesthesia for hydrodissection, the essential components of the system were in place. Eventually, these included a transilluminator/irrigator, which is similar to the present device, and a resector, which was still a modified arthroscopic shaver with a 4.5 mm blade.

Spitz's original experience was reported five years ago.[1] His original description of the technique is very similar to the present-day method with some modifications. "The TriVex System" combination tumescent anesthesia delivery system and illuminator were used to select sites for the local anesthesia. Transillumination was obtained with light from a 45-degree illuminator specifically designed for this purpose. Varicose clusters were extracted by use of a modification of Smith and Nephew EP-1 endoscopic powered tissue dissector. Then, as now, this device is a rotating, tubular inner blade encased in a protective stationary outer sheath. The working opening is placed adjacent to the varicosities, which are then aspirated, morcellated, and removed

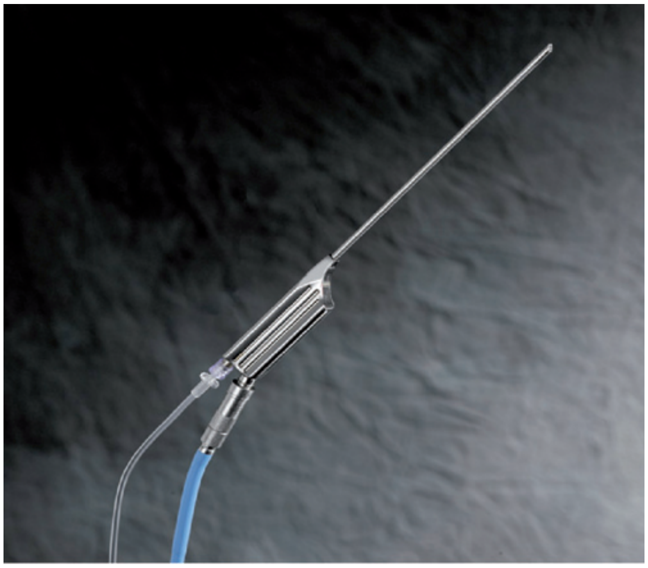


FIGURE 28.1 Original transilluminator/irrigator.

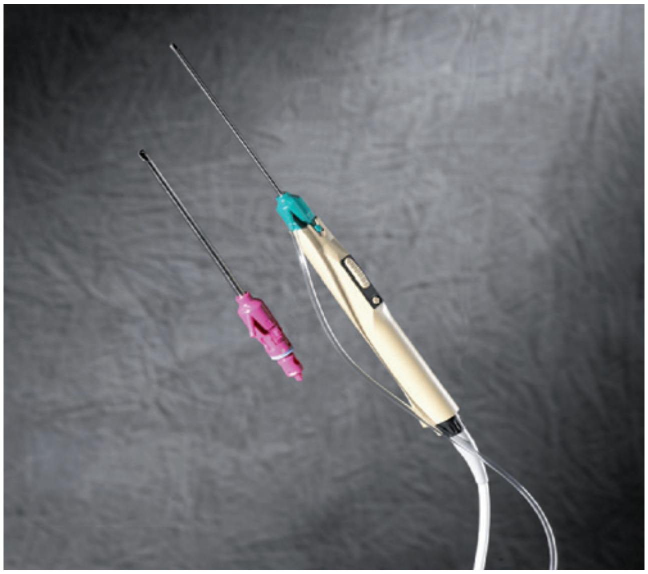


FIGURE 28.2 Original powered resector.

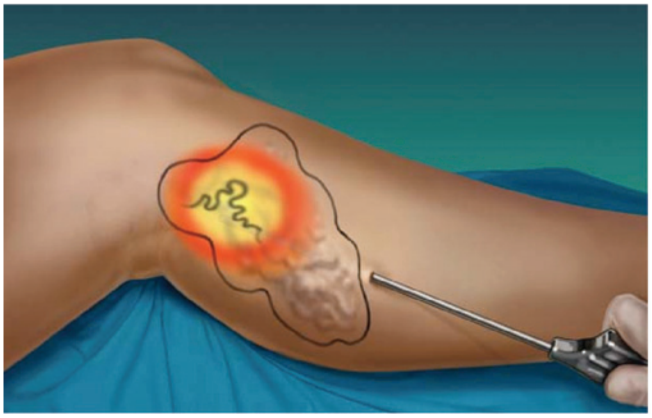
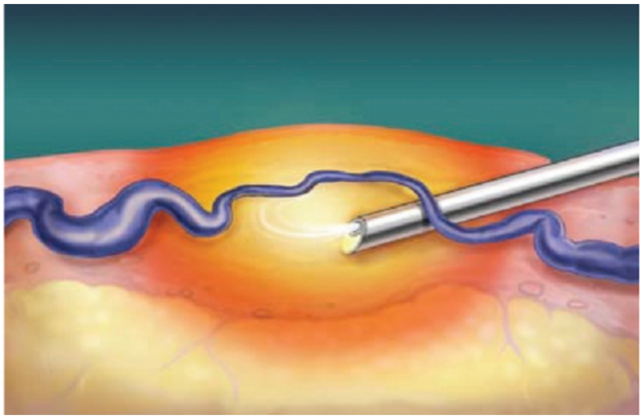


FIGURE 28.3 Instillation tumescent fluid.



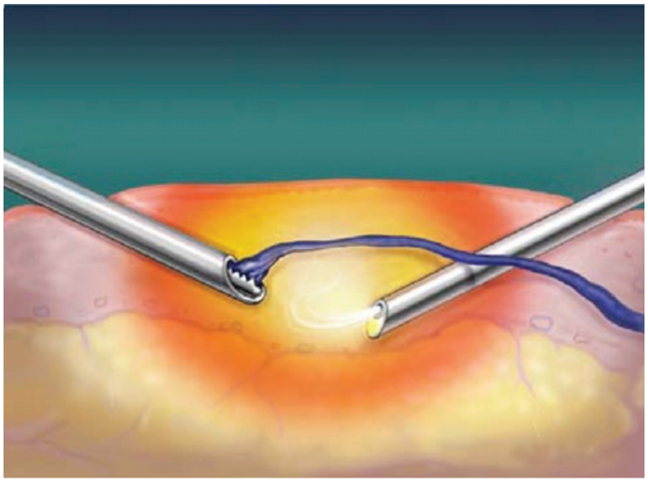


FIGURE 28.4 Resection varicosities.

by irrigation suction. Control of vein removal is through a handpiece that directs the vein fragments into a container connected to hospital wall suction.[1]

As reported, the initial results were encouraging. The operation appeared faster (41 vs. 75 minutes) and required fewer incisions (5.6 vs. 17). Cellulitis, hematoma, significant bruising, and swelling were recorded as complications. However, cosmetic scores appeared acceptable.

The discussion following the initial presentation commented, "Despite knowing that change is constant, who would have thought that change would occur in routine varicose vein surgery. Yet change has occurred. This presentation by Spitz demonstrates ingenuity and imagination in pursuing development of a dedicated tool for better removal of venous varicosities." TriVex was now ready for a larger clinical trial.

FIGURE 28.5 Pre-op marking.

FIGURE 28.6 Transillumination intra op.

INITIAL CLINICAL TRIAL AND TECHNIQUE

The initial clinical trial consisted of centers in the United States (4) and Europe (4), in which we participated.[2] Prior to instituting the trial, Spitz visited each site or the participants visited him to gain hands-on proctored experience. This, of course, insured relative consistency of methodology. There were variations developed on the original theme especially regarding irrigation pressure devices.

The technique ultimately used in the trial was very similar to that described in Spitz's original presentation. For purposes of understanding, the original technique and technology are described next, because these have implications regarding the subsequent modifications. The technique being described is the original method and not the present modification.

Initial patient evaluation is exactly as is traditional in varicose vein surgery. Full duplex imaging is obtained and all abnormal vein segments are identified and marked. The markings are placed around the veins and not directly on the varices themselves (see Figure 28.5). The reason for not placing markings directly over the veins is that these may be misinterpreted under transillumination as residual unresected veins. Saphenous incompetence is managed by surgeon's choice, laser (EVLT), radiofrequency (VNUS), or by traditional stripping.

The operation was done using general, spinal, or laryngeal mask airway anesthesia with the patient positioned in Trendelenburg position. An initial 3 mm incision was made just outside the marked area of varicosities. The transilluminator/irrigator was placed subcutaneously and distal to the level of the veins The room lights were dimmed for better transillumination (see Figure 28.6).

The first stage of tumescence was infused using a mixture of 40 cc of 2% xylocaine and 1 cc epinephrine in a liter of saline. This is infused using a pressure bag, high pressure blood transfuser, or a peristaltic pump as that used for liposuction.

As will be discussed later, infusion techniques became a significant variable.

The tumescent fluid hydrodissects the veins, partially exsanguinates the veins, and allows better diffusion of light in the subcutaneous tissue.

After the first stage of tumescence, the veins are ready for resection. A second 3 mm incision is made, preferably 180º from the first incision. The resector is passed subcutaneously immediately beneath the veins in a more superficial plane than the illuminator (see Figure 28.7). The resector targets the veins and these are suctioned into the rotating blade, morcellated, and removed (see Figure 28.4).

Most of the veins are removed with the first pass. The operator should not go back and forth over a resected area, as more bruising will occur. The skin lying over the area of resection is kept taut to minimize skin trauma and stabilize the veins that are being resected (see Figure 28.8). To treat other areas, the resector is removed and redirected. Shearing through tissue is therefore minimized. To reach more distant areas the resector and irrigator/illuminator ports may be reversed or inserted through other incisions.

After resection, a second stage tumescence is infused. This has a two-fold goal: irrigation and removal of any residual blood and creation of subcutaneous pressure to

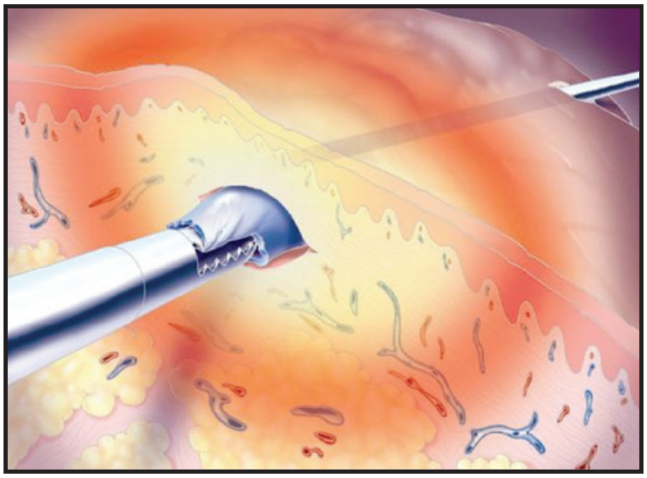


FIGURE 28.7 Level of resector.

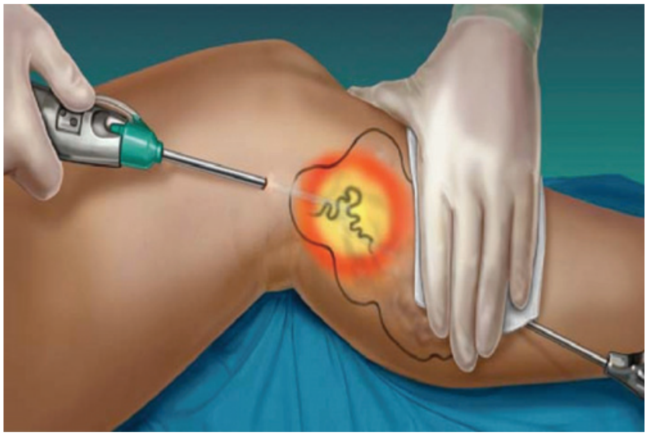


FIGURE 28.8 Resection with skin tension.

tamponade the ends of resected veins. Enough fluid is infused to create a peau d'orange effect on the skin. The incisions are closed with steri-strips and overwrapped with an absorbent compression dressing.

Postoperatively, the leg is redressed on the second or third day, and compression stockings are prescribed for two to three weeks.

Initial visual results are usually good. Bag Balm, an ointment with hydroquinilone, is used with massage to help minimize scarring and hasten subcutaneous healing.

This was the technique and technology for the initial trial. This was also the technique that was taught and used during the initial three years of TriVex use. Results of the clinical trial were good. The procedure was relatively quick: 14 minutes for phlebectomy and 45 minutes for phlebectomy and saphenous excision. The median number of incisions required were three. Most patients were happy with the results. Complications did occur: hematoma, subcutaneous scarring, bruising, and hyperpigmentation were the most notable.

CLINICAL TRIAL AND TECHNIQUE DISCUSSION

Every procedure has a learning curve. Changes were made to address the technique and technology issues that were identified in the initial experience. These led to a better procedure, thus giving the present excellent results.

We entered the maximum number of cases (20) that could be entered into the trial and patients operated upon later in the series did better than those treated earlier. Overresecting and shearing through tissue caused some of the subcutaneous scarring and bruising. In the beginning it was not appreciated by most of us that veins were removed with the first pass of the resector. This lead to overresecting. After a vein segment is resected blood fills that resected channel from either end of the resected vein. This can appear as an unresected vein and the operator may re-resect the area leading to excessive subcutaneous trauma. The resection vein site does appear different from an unresected vein. It appears as if a vein has been smudged and has a less defined outline.

Hematoma and hyperpigmentation are caused by residual trapped blood. The initial technique called for closing incisions with steri-strips or suture to keep the second stage tumescence in the subcutaneous tissue to help tamponade bleeding from the ends of the resected veins. This of course, did not enhance drainage of any residual blood.

CLINICAL TRIAL TECHNOLOGY ISSUES

As mentioned previously, the irrigator/illuminator was used with various pressure infusion devices. This did not allow standard instillation of fluid for tumescence or for evacuation of blood post resection. Various trial centers were able to be highly effective, whereas others could not attain significant flow rates. This lead to residual hematomas.

Blade speeds of 800–1000 rpms were used. In general 4.5 mm (smaller) blades were used. Both of these factors did not allow suction to be applied adequately to the veins to be resected due to the small blade aperture. Some residual segments were left and areas needed multiple passes to resect veins. This enhanced subcutaneous scarring.

The counterintuitive notion of slow blade speeds and larger blades being less traumatic did not surface until later in the experience.

SUMMARY OF INITIAL TRIAL

Despite some of the shortcomings identified earlier, most patients and surgeons participating in the trial were quite happy. The procedure was faster, required less incisions, and was more enjoyable and less tedious than traditional procedures. Cosmetic scores and patient satisfaction scores were acceptable.

EARLY RESULTS AND EXPERIENCE

After the initial clinical trial, training of other physicians began. This consisted of a variety of methods. Didactic presentations were held throughout the country. Training also involved observing cases, hands-on experience, as well as proctoring of initial cases. Many surgeons began to utilize the technique; the appeal being a faster, more complete vein removal with fewer incisions.

As more surgeons became involved, a number of technical and technological issues began to surface. From a technology perspective there was not standardization of irrigation and tumescent infusion. A variety of devices were used, including pressure bags, gravity, blood infusers, laparoscopic irrigators, and peristaltic pumps. These all delivered varying rates and pressures of infusion. The dictum was to use the highest pressure available, but that varied from institution to institution. This led to significant residual subcutaneous blood and, at times, hematomas requiring drainage.

Another technological issue was blade size. Most surgeons utilized the smaller original blade at 1000 rpm. This led to excessive mechanical trauma and less efficiency in suctioning veins into the blade. From a technique viewpoint, some surgeons did not appreciate the damage that a patient could incur if one was rough and swept through the subcutaneous tissue when one was resecting. The concept of "targeted gentle" resection was not always adhered to. Many surgeons continued the pulling and tugging required during traditional techniques.

The instillation of second stage tumescence after vein resection and the closure of incision sites led to trapped blood and fluid, not allowing adequate drainage. The original thinking was that the pressure of tumescence would tamponade the ends of resected veins, and minimize bleeding. What did occur in some cases was prolonged subcutaneous edema from the tumescence. Most edema did resolve over a period of time.

Despite some of these issues, many surgeons gained significant experience and results continued to improve. Groups then began reporting results with very consistent findings.

RESULTS

The original reported results of Spitz et al. continued to be obtained by other investigators. At the core were consistent findings: shorter procedure, decreased number of incisions, similar patient satisfaction, and similar complication rates, when compared to traditional methods.[3–5] Improved results with experience was expected and was echoed by a number of investigators.[5,6] The resection of extensive varicosities was an area in which TriVex was found to be significantly faster than traditional procedures.[3,4] Operative time varied between investigators but most were within the range of 12 to 30 minutes for the TriVex part of the procedure.[2,3,7] This difference became more important and achieved greater statistical significance as the extent of resected varicosities increased.

The initial multicenter safety and efficacy trial had an average phlebectomy time of 14 minutes and the median number of incisions as 3.[2] All other reports showed a significant decrease in incisions ranging from 3.6 reported by Arumugasamy to 4.0 (compared to 18.9) attained by Ray-Chaudhuri et al. in a prospective trial. In the only prospective randomized trial Aremu et al. found a significant difference between traditional (29) and TriVex (5) incisions ($p < .0001$). What is also clear and consistent is the conclusion that post-op pain scores, patient satisfaction, patient cosmetic scores, and complication rates are essentially the same as traditional methods. Ray-Chaudhuri et al. compared post-operative pain scores with the results after 14 days being 2.6 (traditional) and 1.9 (TriVex) (NS). Mean cosmetic scores were also similar 6.9 (traditional) and 5.9 (TriVex) (NS).[3] Scavee, after gaining experience, reported midterm clinical experience.[8] The mean pain score at six weeks was 0 (no pain) for TriVex. Patient satisfaction and patient cosmetic scores showed no significant differences in the two randomized trials.[3,4] This was first pointed out in Spitz's original report. Complications do occur and have been reported. The rates appear to be similar to conventional procedures. Arumugasamy et al. reported that, "bruising was seen in nearly all patients at 1 week and this settled between 6–12 weeks later."[7]

Mackay[9] reported a 66% incidence of perceived complications, including bruising, within the first two weeks following conventional surgery. Aremu et al. in a prospective randomized trial found no difference with regard to bruising, cellulitis, or numbness between techniques. Nerve injury was 3% at one year.[4]

The learning curve has been discussed by a number of investigators. It is no surprise that earlier cases resulted in poorer results and experience improved results. Scavee in his midterm trial results states "our initial clinical experience was associated with a high rate of hematoma formation, especially in the calf region, resulting from our learning

curve. Indeed, as previously described, comparison of our first twenty patients with our second 20 patients revealed a significant reduction in hematoma (17 vs. 6, p = 0.0005)."[8]

Shamiyeh et al. recognized that in comparing 1000 conventional phlebectomics to his first 41 TriVex procedures, a significant learning curve existed and that it was somewhat unfair to make the comparisons. They also heralded some technique changes to minimize complications. In summary, a learning curve of 10 to 20 cases was acknowledged.

TriVex can and has been used to treat other conditions such as venous stasis ulceration.[10] It also has been shown to have a positive effect on incompetent perforating veins.[11] It is one of the tools of minimally invasive vein surgery.[12]

In conclusion, results tend to be consistent: fewer incisions, shorter operative times, more complete removal of varices. These results all are accomplished with complication rates comparable to traditional procedures. All the reported results, whether they be safety and efficacy trials, randomized trials, or prospective randomized control trials, have come to similar conclusions.

FIGURE 28.9 TriVex II System.

LESSONS LEARNED: THE TRIVEX MASTERS MEETING

Even with the very consistent and acceptable results, it was the consensus of surgeons with significant experience that improved results could be attained. A meeting of the 15 most experienced TriVex users was convened January 2003. Field testing of the second generation TriVex device had already occurred at a few centers. The goal of this meeting was threefold: standardize new techniques, standardize new technology, standardize the training of these two. What evolved from this meeting was a new technique and technology that attained significantly improved results from what was already an acceptable procedure.

The technique issues of hematoma, hyperpigmentation, bruising, and subcutaneous scarring were addressed. Technology issues such as infusion rates and pressures, blade size, blade speed, drainage, tumescent infusion level, and compression were standardized. Training, teaching, and proctoring were other issues discussed. The following is the most up-to-date method for TriVex vein resection, which is the standard at the time of this writing. Much is similar to the original technique developed by Spitz. The changes and added features will be highlighted.

TRIVEX II: NEW TECHNIQUE AND NEW TECHNOLOGY

The significant changes to the technology consisted of the TriVex II system (see Figure 28.9). This system has peristaltic infusion pumps for both tumescence and the resector. This overcomes one of the main shortcomings of the original system: lack of adequate pressure and flow rate for tumescent infusion. The variability in infusion led to some early centers not obtaining enough clearance of subcutaneous blood leading to hematoma and pigmentation. A brighter light source was included, which allowed better visualization and more complete vein removal. Minor ergonomic changes were incorporated into the resector and illuminator/irrigator.

The recommended technique changes evolved during the consensus meeting of the TriVex Masters. Spitz had laid much of the groundwork. Others had come to similar conclusions. The changes in technique addressed issues of bruising, hematoma, pigmentation, and subcutaneous scarring. Trauma to the tissue was further minimized with the utilization of a larger blade (5.5 mm) and slower blade speeds (300–500 rpm) in a pulsed manner. At first it seems counterintuitive that larger blades and slower speeds cause less trauma. The larger aperture of the blade and slower speeds allow more time for suction to be applied to the veins. Therefore, suction does much of the resecting rather than the shaver. This causes less subcutaneous trauma and scarring. The concept of enhanced drainage was introduced. Instead of closing incisions to contain tumescence (and residual blood), wounds are left open. Additional drainage sites were made with either a #11 blade or 2–3 mm dermal punch (see Figure 28.10). The concept of enhanced drainage is a 180-degree switch from the original technique. It has solved the hematoma and pigmentation issues (see Figure 28.11). Patients recover sooner with less discomfort.

FIGURE 28.10 Drainage sites.

The third change in technique is the installation of third-stage tumescence in the subcuticular tissue above the level of resected veins. This adds to the external tamponade of compression wrapping (see Figure 28.12). The tumescence is infused with #18 spinal needle attached to the same pump of the TriVex II System. Much more tumescence is utilized during these procedures (1–1.5 liters), with most being used as irrigation to clear the resected vein channels of residual blood and not absorbed by the patient. Thus, most tumescence is washed out prior to completion.

SUMMARY OF PRESENT TECHNIQUE

1. Pre-Op
   - Doppler evaluation
   - Mark around areas of resection
2. Preresection
   - Infuse first stage tumescence below levels of veins
   - Patient in Trendelenberg
   - Tumescence partially exsanguinates veins and fixes veins
3. Resection with Transillumination
   - Larger blade (5.5 mm)
   - Slower resector speeds (300–500 rpm)

FIGURE 28.11 Post-op result.

FIGURE 28.12 Third-stage tumescence.

- Pulsed (on/off) resection
- Keep skin taut with free hand
- Targeted resection—no shearing, directed subcutaneous channels

4. Post-resection: Second Stage Tumescence
   - Transillumination visualization
   - Place illuminator/irrigator in channels of resected veins
   - Irrigate residual blood
   - Place further drainage sites—2–3 mm dermal punch or #11 blade
   - Obtain clear effluent
5. Third Stage Tumescence with Transillumination
   - #18-gauge spinal needle
   - Place in subcuticular plane
   - Obtain peau d'orange effect on skin
6. Post-Procedure
   - Wrap with compressive dressing
   - May use ABDs, Kerlex, Ace, Coban, etc.
   - Ambulate immediately
   - Unwrap two days post-op
   - Compression stockings for two to three weeks

DISCUSSION

TriVex has evolved. The present technique yields extremely acceptable symptomatic and cosmetic results. As already mentioned in the results section, most patients and surgeons are happy. These studies were done with original technology and original technique. The majority of surgeons now use new technology and new technique. Results are better with the new method. As of this time, studies have not been done to quantitate this impression. What are some of the questions currently asked about TriVex?

- What is a learning curve? One can learn to resect veins after one or two cases. The key question is how many cases will it take to attain cosmetic results equal to an experienced TriVex surgeon? Approximately 10 to 20 cases are necessary to optimize your results.
- Can TriVex be used to resect the Great or Small Saphenous vein? No, these veins are too deep and cannot be visualized. More importantly, significant saphenous or sural nerve injury is possible.
- Can I use TriVex with other vein procedures? Yes, whatever procedures you would normally perform in conjunction with traditional varicose vein excision can be done with TriVex (e.g., laser or radiofrequency endovenous ablation, stripping, SEPS, etc.).
- What about difficult areas such as the knee, ankle, pudendal? These are all good candidates for TriVex after experience. The initial first stage tumescent hydrodissects the veins away from the underlying bony area.
- Is placement of incisions critical? Yes and no. With experience one can better "hide" incisions. For example, varicose veins over the anterior thigh or shin can be resected by incisions placed medially on the inner aspect of the thigh, thus hiding them. With traditional techniques, incisions must be placed directly over the veins, making them more visible.
- Are there any varicose veins for which TriVex cannot be used? TriVex works well for all varicose veins regardless of size or location. In fact, postsclerotic friable varicose veins are better removed with the suctioning and morcellating effect as compared to the hook or clamps of traditional procedures. The tumescence helps to partially exsanguinate large veins, size does not matter. Large veins are removed as easily as smaller veins.
- Does TriVex require general or regional anesthesia? No. This author and other experienced TriVex users perform most procedures using local tumescent and mild intravenous sedation. Since late 2004 we have performed almost all procedures with local anesthesia and sedation. When learning TriVex it is preferable to

begin with laryngeal mask airway or short-acting regional since these patients should ambulate soon after procedure completion.

- What are the contraindications to TriVex? These are the same as those for any venous surgery: acute DVT, active thrombophlebitis, inability to ambulate, and so on. There are no specific contraindications relative to TriVex.
- What are some of the more common complications utilizing the newer technique and technology? Temporary subcutaneous sensory nerve parastheias occur, hematoma may still occur but is now in the range of 1%, and bruising lasting longer than one to two weeks occurs in approximately 5% of patients. Long-term subcutaneous scarring has almost been totally eliminated with slower, larger blades. The TriVex technique also has been used in countries aside from the United States and Europe.[13,14]

SUMMARY

TriVex is a mechanical method to remove tributary varicosities. As with any procedure it has its unique qualities and quirks. Can TriVex be used for every varicose vein? Yes. Does this author utilize TriVex for all varicose veins? No. Personal experience and data elucidated in the results section indicate that the real statistical advantage occurs with large extensive veins, smaller extensive veins, extensive veins, and postsclerotic veins. In these clinical settings the procedure is significantly shorter and always involves less incisions. For small localized varicosities, I tend to employ foam sclerotherapy or microphlebectomy.

What studies also reveal is that patients are as happy with TriVex as traditional techniques. Surgeons tend to be happier with TriVex for extensive varicosities due to less operating time, less incisions, and better visualization lending to less residual varicosities. There is no need to apologize for using a technique that gives as good a result for patients and is more advantageous to the surgeons. Our time is important. The time saved for extensive varicosities outweighs the disposable cost of $210 to $220. Operative time and costs are also reduced. The facility saves money.

What is the future? Procedures all done with local tumescent and oral/IV sedation in an office setting. Trials are now under way to address these issues.

In conclusion, TriVex is a method of vein removal that surgeons should be familiar with. It has its place for certain clinical settings. This book and this chapter underscore the variability and complexity of treating vein disease. The vein surgeon should strive to be as complete as possible in knowledge and ability. It is my hope that this chapter added to this goal.

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CHAPTER

29

Endovenous Laser (EVL) for Saphenous Vein Ablation

THOMAS M. PROEBSTLE

INTRODUCTION

Endovenous laser treatment of saphenous veins developed during the 1990s. However, it took until 2001 when Min, Navarro, and Bone published their first relevant paper about endovenous laser treatment of the Great Saphenous vein[1] that brought the technique to the attention of the whole phlebology community. Endovenous laser treatment of the Small Saphenous vein was not even described before 2003.[2] Today endovenous laser treatment of saphenous veins offers the patient an outpatient procedure that frequently enables him or her to return to occupational activity the same day or the day after the procedure. Additionally, because no relevant injury to the skin happens during endovenous laser treatment, the cosmetic outcome is usually excellent. In the last few years our understanding about mechanisms of action, the role of various laser wavelengths, proper laser energy and treatment efficacy, and side effects and complications increased tremendously, and even a systematic review about endovenous laser treatment has been published recently.[3]

MODE OF ACTION OF ENDOVENOUS LASER TREATMENT

The final goal of endovenous laser treatment is the ablation of pathological reflux of blood by durable occlusion of the vein lumen. In general this can be achieved either by shrinkage of the vein until the vein lumen has vanished completely, or by substantial damage to the endothelium and inner vein wall leading to secondary occlusion of the lumen by a clot, similar to the effect of a sclerosing agent.

Steam Bubbles and Vein Wall Damage

Initially, diode lasers with wavelengths of 810 nm,[1] 940 nm,[1,4] and 980 nm,[5] but also a 1064 nm Nd:YAG solid state laser,[6] were used for endovenous laser treatment. All these laser wavelengths are predominantly absorbed by the oxygenized and deoxygenized hemoglobin of red blood cells present within the vein lumen. Water absorption does not play a major role with these wavelengths. Remarkably, the absorption of hemoglobin in this part of the electromagnetic spectrum is high enough that a blood film of a thickness of only 200–300 microns absorbs more than half of the emitted laser energy.[7] Actually, during endovenous laser treatment, these absorption characteristics, in combination with typical values of laser irradiance emitted by the predominantly used flat tipped laser fibers of 600 micron diameter, leads to the formation of steam bubbles[4] within the vein lumen. These steam bubbles are not static but they are in vigorous movement once they start to be produced (see Figure 29.1). A mixture of hot blood and steam results in a kind of a bubble-jet stream, responsible for convective heat transfer to remote parts of the vein lumen, which otherwise would not be accessible to the direct impact of the laser beam. To give an easily understandable picture of this process, this mixture of bubbles and blood can be compared to the milk foam produced by an Italian cappuccino machine.

Certainly, where the laser beam emitted by the flat end of the fiber tip was directed straight toward the inner vein wall, mechanisms of high energy absorption in small tissue volumes leading to vaporization of tissue are present as well. This can cause partial or complete perforation of the vein wall including carbonization of the adjacent parts of the vein.[4] As mentioned already, these types of endovenous vein wall damage can be observed only in those parts of the vein

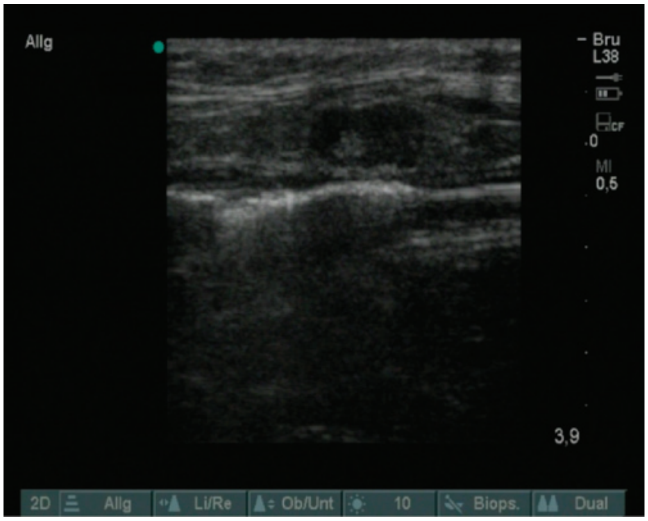

FIGURE 29.1 Jet-like steam bubble formation during endovenous laser treatment of the proximal Great Saphenous vein with a 600 micron diameter fiber and a 940 nm laser set to 30 watt continuous.

that were hit by direct laser beam impact. Other remote parts of the vein circumference cannot be damaged as severely during laser treatment; even with up to three times repetitive treatment of the same Great Saphenous vein, a thermal damage involving the media layer of the vein can be achieved only in less than 40% of the vein circumference.[8]

Vein Wall Shrinkage and Thrombotic Occlusion

Substantial heat transfer to the vein wall leads to significant shrinkage of vein wall collagen fibers and consecutive reduction of the vein lumen. This fact is well known from radiofrequency closure of saphenous veins. However, a comparative animal study between radiofrequency closure and endovenous laser treatment[9] showed that this vein wall shrinkage does not occur automatically with laser treatment. Within the setting of the previously mentioned experiment using an 810 nm diode laser in a pulsed fashion, multiple vein wall perforations and only limited vein wall shrinkage could be observed. Our own studies[10] showed that vein wall shrinkage directly depends on the delivered linear endovenous energy density (LEED), given in Joule per cm. For example, a LEED of 80 Joule per cm leads to an immediate vein wall shrinkage of about 30%. If as much as 150 Joule per cm vein length were delivered, 50% of shrinkage of the vein wall can be achieved.

The amount of vein wall shrinkage seems to be important because the remaining lumen of the vein after laser treatment is subject to occlusion by endovascular clot formation. This clot later could be subject to recanalization, and it could be assumed that the larger the clot diameter the higher the

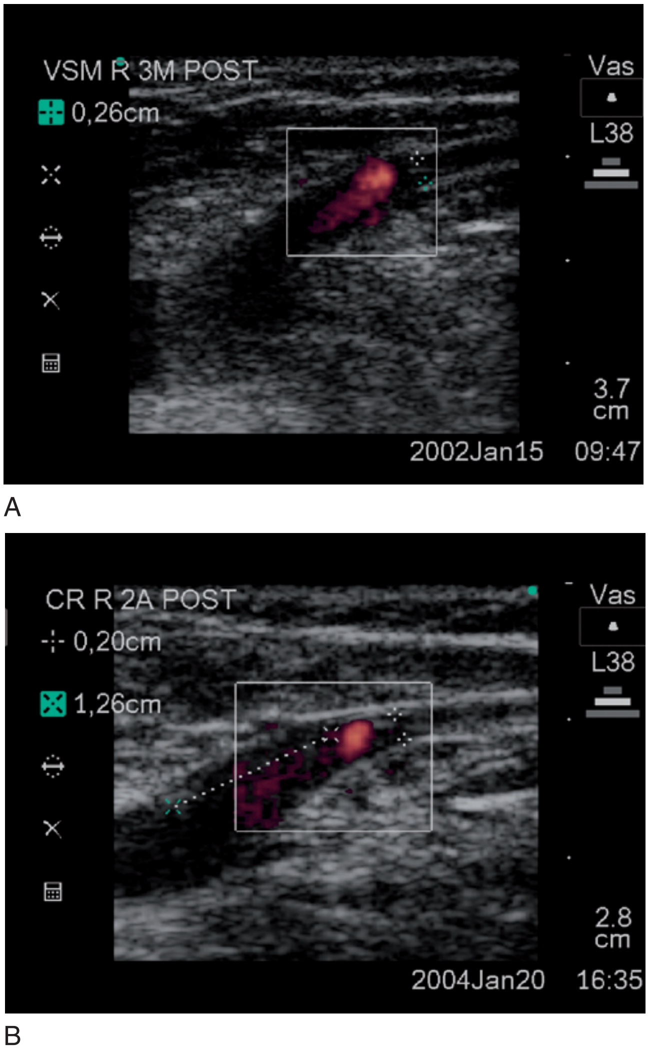

FIGURE 29.2 Occlusion of the GSV 3 months (**A**) and 2 years (**B**) after endovenous laser treatment (940 nm, 15 watt, stepwise fiber pullback).

risk for subsequent recanalization. Ideally, such a thrombotic occlusion of the saphenous vein after endovenous laser treatment is replaced by a fibrotic cord that frequently can be detected even years after laser treatment (see Figure 29.2).

Laser Wavelength

Laser wavelength actually seems not to be too important for the success of endovenous laser treatment of saphenous veins. At least in the range between 810 nm and 980 nm neither hemoglobin absorption[7] nor the resulting steam bubbles depended on wavelength. Steam bubble formation was shown to be correlated just to the emitted amount of energy in Joule.[11] The only wavelength in regular clinical use, which might deserve special consideration, is 1320 nm. At this wavelength hemoglobin absorption does not play a role any more and water absorption is the dominant

mechanism. As such, the vein wall is gently heated and shrunken without perforations, translating in less frequent and also less intense adverse events as described later.

PERFORMING ENDOVENOUS LASER

Performing endovenous laser treatment of saphenous veins can be split in the sections 1) vein access and fiber placement, 2) anesthesia, 3) delivery of laser energy, and 4) post-interventional care.

Placement of the Laser Fiber

Getting easy vein access starts with a comfortable temperature in the theater room to avoid vein spasm in sensitive, frequently young female patients. The patient is then cleaned, draped, and placed on the table in a reverse Trendelenburg position to additionally fill the veins by gravitational forces. The ultrasound probe and the ultrasound keyboard are also covered sterile. To preserve the minimal invasive character of endovenous laser treatment at its most, vein access by ultrasound controlled puncture is the appropriate way; however, stab incision and exposing the vein to the skin surface by use of a phlebectomy hook is an alternative technique. The location of vein access is close to the distal point of pathological reflux and can be achieved by using an 18G venule. A teflon-coated guidewire and a 5F angiocatheter used as a sheath help to place the laser fiber tip between 1 and 2 cm distal to the saphenofemoral junction. In case of treatment of the Small Saphenous vein it is sufficient to place the fiber tip at that point where the small saphenous vein leaves the fascia toward the popliteal vein. The precise position of the tip always needs to be controlled by B-scan ultrasound.

Anesthesia

Endovenous laser treatment can be performed under any kind of anesthesia. Tumescent local anesthesia, however, has the advantage of not only providing sufficient anesthesia but also forming a heat shield around the vein. It protects delicate structures like nerves and other perivascular tissue, and most important in slim patients, the skin. Furthermore, under tumescent local anesthesia the patient still can bring pain originating from nerve damage to the attention of the physician before durable nerve damage can happen. This is particularly relevant when treating the Small Saphenous vein running close to the sural nerve.

For tumescent local anesthesia different mixtures are reported. Either lidocaine or prilocaine are suitable in concentrations between 0.05 and 0.2%. A total volume of 100–500 cc, depending on the length of the vein to be treated, is needed for ultrasound-controlled perivenous infiltration, most conveniently injected by the use of a motor-pump.

Schedules of Laser Energy Delivery

Energy delivery during endovenous treatment of saphenous veins is not standardized. Laser energy can be delivered either in a pulsed or continuous fashion in combination with stepwise or continuous fiber pullback, respectively. Published schedules include laser pulses of 1–2 sec duration in combination with stepwise pullback of the laser fiber of 1–5 mm between single laser pulses. The laser power is set between 8 and 15 watts with pulsed laser treatment. Specific recommendations of laser device manufacturers may be more specific for individual laser devices. If continuous fiber pullback is used it can be performed either manually or by the use of motorized pullback devices in case of the 1320 nm laser. In general, typical pullback speeds are in the range between 0.5 and 3 mm/sec and typical settings of the laser power range between 5 and 30 watts.

Recent publications suggest, regardless whether stepwise or continuous fiber pullback is used, that the LEED value is around 80 joule per cm vein length.

Post-Interventional Care

Post-interventional care of endovenous laser patients is variable around the world. Our schedule includes excentric compression over the course of the treated vein for one day and graduated compression stockings (30 mmHg) for a total of eight days. Additionally, low molecular weight heparins (dalteparine 2500 IU s.c.) were administered, also for eight days, once daily starting immediately after the procedure. Patients were advised to return to normal physical activity immediately after the intervention and nonsteroidal antiphlogistics like diclofenac or ibuprofen were prescribed for use at the discretion of the patient.

SELECTION OF PATIENTS

Selection of patients for endovenous laser treatment of saphenous veins is very simple. Any patient foreseen for a stripping procedure, either of the Great or Small Saphenous veins, is suitable. Placement of a guidewire and laser fiber is at least as easy as placement of a wire-stripper. Patients with acute disease who therefore would not receive high ligation and stripping procedures are usually also not candidates for endovenous laser treatment. However, endovenous laser can additionally be performed in some patients not really well-suited for high ligation and stripping. Such patients are those taking coumadin or phenprocoumon for various reasons. They can be treated without withdrawal of anticoagulation. Also patients with peripheral arterial disease or those with a peripheral venous bypass are suitable candidates. They can be treated the same way as normal patients apart from the point that compression stockings or other

circular compression bandages have to be avoided after the procedure. Compression is limited to excentric compression and inpatient follow-up could be taken into account in such cases.

Like for surgery there are conditions that make a patient not, or at least less, suited for endovenous laser. Examples for these conditions are a prior thrombophlebitis of the saphenous vein or earlier sclerotreatment of it. In such cases parts of the vein might be still occluded or have been subject to multiluminal recanalization, so that the laser treatment cannot succeed in complete ablation of all parts of the vein recognized by duplex ultrasound.

Pronounced tortuosity of the saphenous vein or the presence of aneurysmal dilatations generally does not prevent endovenous laser treatment; particularly, there is no diameter limit for endovenous laser. However, advancement of the guidewire may be difficult in these cases and if advancement of the wire is still impossible with skin stretching maneuvers, a second vein access may be necessary to allow treatment of the whole length of the vein.

Another disputable issue is the laser treatment of extremely superficial, immediate subdermally located saphenous veins. This is sometimes the case in slim patients with a body mass index around 20 or below, or if the saphenous vein leaves its fascial compartment relatively proximal. In these cases the deeper located proximal part of the vein can be treated by laser, the distal superficial part can be removed by miniphlebectomy to avoid the long-lasting presence of a subdermally located indurated vein that later might cause secondary hyperpigmentation of the overlying skin.

EFFECTIVENESS OF ENDOVENOUS LASER TREATMENT

Long-term results about endovenous laser treatment of the Great Saphenous vein are still missing to date; therefore, success can be reported only with respect to immediate postprocedural ablation of the vein and with respect to recanalization events during midterm follow-up. Other interesting questions like five-year success rates or questions about randomized prospective comparison to traditional surgery cannot be answered today. Also the questions whether endovenous laser treatment is not associated with future neoangiogenesis or if the pattern of future disease progression of venous disease is generally influenced, remain open at present, even if there is an interesting publication suggesting one mechanism for recanalization of veins after endovenous ablation.[12]

Immediate Success Rate of Endovenous Laser Treatment

Published data upon immediate closure of the Small Saphenous vein is still rare. Success rate of endovenous laser treatment in 39 Small Saphenous veins in which vein access was obtained was 100% at day one.[2] Also complete occlusion of the Great Saphenous vein at day one or during week one after the procedure should be natural. However, early studies[13,14] did not report a 100% success rate; it was around 97%. This was corroborated by our own early studies,[4,15] but in our hands the problem was overcome when we started to treat saphenous veins with higher LEED values in the range between 80 to 100 joule per cm vein length. This was after understanding that the amount of energy delivered per cm vein length plays a central role for treatment success.[15] With a setting of 30 watt continuous laser power (940 nm) and a continuous pullback speed of 3 mm/sec,[10] a 100% occlusion rate of the treated vein segment at day one after laser treatment could be observed.

Recanalization during Midterm Follow-up

Durable occlusion of the treated saphenous vein segment is certainly a central goal of endovenous laser treatment. However, recanalization of the Great Saphenous vein can be observed and frequently it seems to be associated with low energy delivery during treatment.[15] Figure 29.3 displays a so-far unpublished plot of otherwise published original data about three months follow-up of continuous laser treatment of Great Saphenous veins.[15] It clearly displays that recanalization is associated with low LEED values, and furthermore that veins with greater diameter require the delivery of more energy to stay occluded during the first three months after treatment. The line drawn in Figure 29.3 is the result of linear regression analysis of open boxes showing a slope of about 10 joule per cm GSV diameter. This indicates that

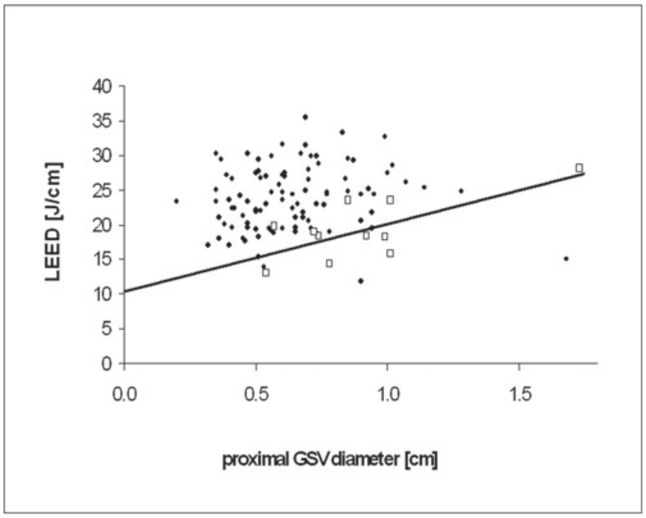

FIGURE 29.3 Plot of the linear endovenous energy density (LEED) versus the proximal diameter of the Great Saphenous vein. Dots resemble veins still occluded, open boxes resemble veins already recanalized 3 months after endovenous laser treatment (15 watt, continuous). The line is the result of linear regression analysis of the data of open boxes and is described by the formula $y = 9.7x + 10.6$.

a 15 mm diameter vein requires 10 joule of laser energy more per cm vein length to stay occluded at three months compared to a 5 mm diameter vein. Recent publications indicate that the administration of a LEED of 80 joule per cm vein length helps to reduce the frequency of recanalization events during short term follow-up.[10,16,17]

Relevant studies on short and midterm follow-up are put together in a recent systematic review.[3] Unfortunately, data on midterm follow-up of at least one year after endovenous laser treatment are still rare. The largest study reporting on 121 procedures at 24 months showed an occlusion rate of 93.4%.[14] Other studies reporting a 12-month follow-up demonstrate occlusion rates of 95.2% (N = 125)[18] and 87.9% (N = 107).[19] In our most recent experience, 12-month results were improved to above 98% occlusion rate (N = 91) after introduction of 30 watt high LEED treatment.[10]

Early recanalization of the Small Saphenous vein is not reported so far,[2] but follow-up interval in this study of 37 followed legs was only median six months.

TABLE 29.1 Adverse Effects—Percentage of Affected Legs, Median [min–max] Duration in Weeks According to Laser Schedule

Laser protocol	Continuous 30 watt 940 nm			Continuous 8 watt 1320 nm		
Number of treated legs	N = 136 (100%)			N = 33 (100%)		
Recanalization rate (3 months)						
partial	0%			3% (n = 1)		
complete	0%			0%		
No side effects any time	2%			18%		
Ecchymosis	81%	2	[0.2–4]	61%	2	[1–4]
Pain	81%	1.2	[0.1–12+]	50%	1.5	[0.1–2]
Analgesics	67%	0.3	[0.1–4]	36%	1	[0.1–2]
Induration along vein	64%	4	[0.2–12+]	46%	2	[0.5–4]
Phlebitic reaction	13%	1	[0.2–2]	7%	1.4	[0.7–2]
Paresthesia	12%	3	[1–12+]	14%	1	[0.2–3]

COMPLICATIONS AND ADVERSE EVENTS

Adverse Events

Frequently occurring adverse events after endovenous laser treatment with wavelengths between 810 and 1064 nm include ecchymosis, induration, and pain. Ecchymosis related to endovenous laser is difficult to be assessed, because frequently it is performed in combination with other techniques, producing ecchymosis like Muller's phlebectomy. Under these conditions, ecchymosis rates of 100% are reported most frequently.[3] Only laser treatment of the Small Saphenous vein was associated with a lower rate of ecchymosis of 41%, but in this study phlebectomy was not combined with endovenous laser treatment.[2]

Induration after endovenous laser of saphenous veins is reported in 34% after treatment of the Small Saphenous vein, but in 50 to 100% after treatment of the Great Saphenous vein.[3] Induration frequently occurs a few days after laser treatment—which is sometimes severely irritating to the patient—and continues most likely for one to three weeks thereafter. It frequently is associated with a feeling of tissue shortening for the patient running along the inner thigh most irritating at full extension of the leg. This process most likely is due to the formation and shortening of an inner scar and its concomitant inflammatory processes. Nonsteroidal anti-inflammatory drugs improve symptoms dramatically and are also a good choice for any other treatment related pain.

Less frequent adverse events related to endovenous laser treatment of the Great Saphenous vein are phlebitis and paresthesia. Phlebitis at the treated leg can be observed in 3 to 12% of cases[3] and, in our hands, responds well to nonsteroidal antiphlogistics and prolonged compression therapy. Paresthesia is not consistently reported in all studies but certainly occurs in the range of 1 to 10%.[3] In our observation paresthesia is most likely to happen at the distal leg and most likely resolves spontaneously within less than three months. In only one study the rate of paresthesia exceeded 30%,[6] but in this study extraordinarily high LEED values were delivered along the vein and even skin burns were observed in conjunction with that.

Interestingly, the 1320 nm wavelength seems to be associated with a lower frequency of adverse events[20] even if the delivered values for LEED are comparable to those delivered with diode laser treatment. Table 29.1, which is extracted from a more detailed description,[21] shows that frequency and maximum duration are reduced for pain and induration. However the rate for paresthesia remains unchanged as—given by their natural course—durations for ecchymosis and phlebitis are not.

Complications

Relevant complications reported with endovenous laser treatment of saphenous veins are rare. The most important complications are deep vein thrombosis and clinically inapparent thrombus protrusion into the deep vein system as a special finding related to endovenous procedures. One anecdotal report exists about the formation of an arteriovenous fistula in the popliteal region after treatment of the Small Saphenous vein.[22] The detection of deep vein thrombosis is related to ultrasound B-scan examinations in regular intervals after endovenous laser treatment, which is not performed with the same intensity in all studies. In our own series,[2] we observed one case of a popliteal vein thrombosis after laser treatment of the Small Saphenous vein in a patient with the concomitant diagnosis of polycythemia vera. One interesting phenomenon of endovenous procedures seems to be the thrombus protrusion from the treated saphenous vein

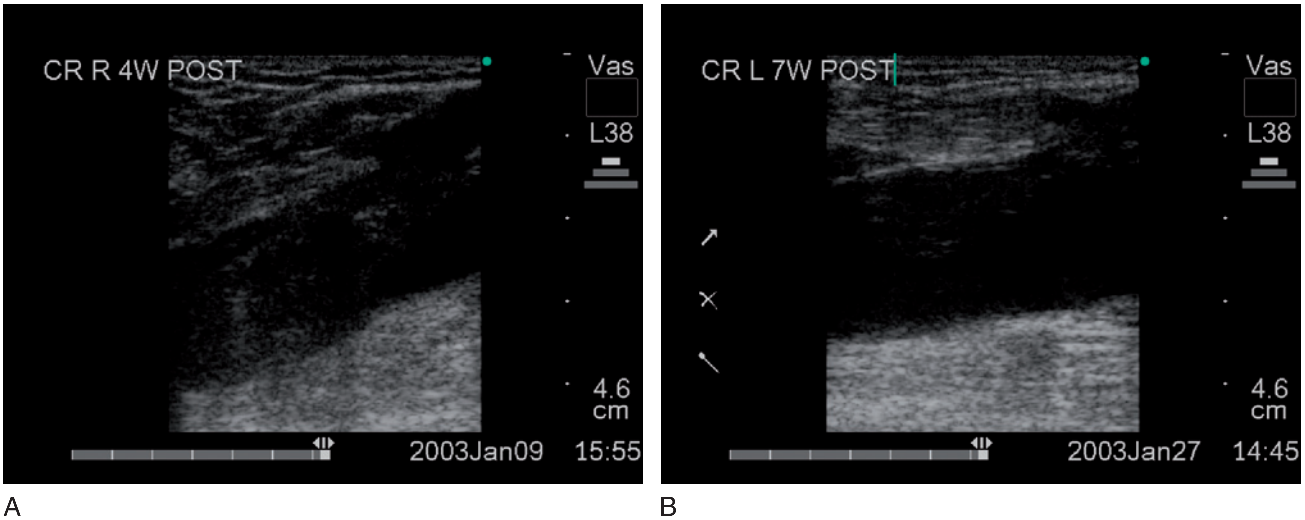

FIGURE 29.4 Thrombus protrusion detected 4 weeks after endovenous laser treatment of the Great Saphenous vein (**A**) showing marked retraction 3 weeks later (**B**).

into the common femoral vein. It was recently reported in three of 54 limbs (5.6%) after endovenous laser cases but resolved without further complications under anticoagulation.[23] Remarkably, despite regular duplex scanning after endovenous laser from the very beginning, in five years we recorded only one case of thrombus protrusion. This single patient, remarkably, stopped his low molecular weight prophylaxis two days after the procedure. Thrombus protrusion was detected four weeks after the procedure and showed retraction three weeks later under anticoagulation with phenprocoumon (see Figure 29.4).

ENDOVENOUS LASER COMBINED WITH OTHER TECHNIQUES

Endovenous laser treatment of saphenous vein can be combined with any other technique to the discretion of the phlebosurgeon. These techniques include Muller's phlebectomy, sclerotreatment of any kind, perforator surgery, SEPS, and endovenous laser occlusion of incompetent perforators. No need to mention that any other pathological reflux in the groin, like reflux in the anterior accessory Great Saphenous vein must be treated concomitantly to ablation of the saphenous vein. Certainly, this also can be done by endovenous laser treatment. However, some surgeons are convinced by the role of subtle ligation of the Great Saphenous vein and all other superficial inguinal veins at the saphenofemoral junction. Therefore they perform a crossectomy in conjunction with endovenous laser treatment of the Great Saphenous vein. In the meantime some examples can be found in the literature for such a strategy.[6,8] However, results of larger comparative trials randomizing endovenous laser against endovenous laser plus crossectomy would be of great help in future discussions.

CONCLUSION

In conclusion, endovenous laser of saphenous veins has left the stage of an experimental procedure, and many details have become obvious, which helped to optimize treatment results. However, prospective randomized trials of endovenous laser treatment versus traditional surgery, versus high ligation performed at the same treatment session, or against other endovenous techniques like radiofrequency closure or sclerotreatment are still missing but urgently needed.

Acknowledgment

Thanks to Drs. Sylvia Herdemann, Doendue Guel, and Thomas Moehler for providing tremendous amounts of follow-up data of endovenous laser patients.

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CHAPTER

30

Effects of Different Laser Wavelengths on Treatment of Varices

LOWELL KABNICK

INTRODUCTION

Varicose veins are a common problem in the United States, affecting mostly women and those over age 50.[1] They may be benign or painful, disabling, unattractive, and dangerous to patient health. Varices arise when the valves in superficial veins malfunction, causing deoxygenated blood to reflux and pool and the veins to swell under increased pressure, usually in the lower extremities. Insufficiency of the Great Saphenous vein (GSV) frequently is found to be the cause, although reflux of the Small Saphenous vein (SSV), perforator veins, and junctional tributaries also may lead to varicose veins.

Traditional treatment for varicose veins involves invasive surgical ligation and stripping of the affected vein; although effective, this approach carries all the risks and expenses of surgery and requires prolonged and complicated recovery periods.[1,2] In recent years, minimally invasive endovenous laser ablation (EVLA) and radiofrequency (RF) ablation have emerged as effective outpatient treatment approaches that enjoy greater patient acceptance compared to surgical stripping.[3] Both methods deliver electromagnetic energy to destroy the vein, although their mechanisms of action do differ.[4]

This chapter focuses on EVLA, a short procedure requiring local anesthesia only. EVLA produces excellent cosmetic results and reductions in preoperative symptoms with no impact on patient mobility and almost no complications.[5–10] In addition, EVLA appears to be slightly more effective than RF in the short term,[10] and is less expensive than either RF or stripping.[11]

EVLA, first described in 1989,[12] involves the intravenous placement of a laser fiber and the controlled release of thermal light energy, damaging the endothelium and leading to thrombosis and resorption of the vessel. In 2002 the FDA approved EVLA for the treatment of varicose veins,[1] and today lasers of several wavelengths are available for use, all of which produce excellent results. Nonetheless, some differences have been noted, particularly in terms of short-term outcomes such as bruising and postprocedural pain. This chapter describes the basics of lasers and EVLA, then compares results among lasers of different wavelengths, including data from a recent clinical trial.

LASER BACKGROUND

Since the first working laser was made in 1960 at Hughes Research Laboratories in Malibu, California,[13] laser technology has been applied to endeavors as varied as large-scale engineering projects and microscopic surgical procedures—depending on its design, a laser can cut through steel or make incisions smaller than the size of a cell. Today, lasers are familiar sources of focused light energy, useful in medicine, technology, and meeting presentations.

The word laser is actually an acronym for Light Amplification by Stimulated Emission of Radiation. Light in this context refers not only to visible light, but to the entire spectrum of electromagnetic radiation, of which visible light is only a small part. Each type of light has a specific wavelength, which determines its properties (see Table 30.1). For example, light with a wavelength of 410 nm is seen as violet, whereas light of 680 nm is seen as red.[14] Beyond the range of visible light are wavelengths shorter than we can see—ultraviolet, gamma, and x-rays—and wavelengths longer than we can see—infrared, microwaves, and radio waves. The lasers discussed in this chapter emit infrared light with wavelengths ranging from 810 nm to 1320 nm.

TABLE 30.1 Spectrum of Electromagnetic Radiation[16]

Type of wave	Wavelength (cm)
Radio	<10
Microwave	10 to 0.01
Infrared	0.01 to 7×10^{-5}
Visible	7×10^{-5} to 4×10^{-5}
Ultraviolet	4×10^{-5} to 10^{-7}
X-ray	10^{-7} to 10^{-9}
Gamma Ray	$<10^{-9}$

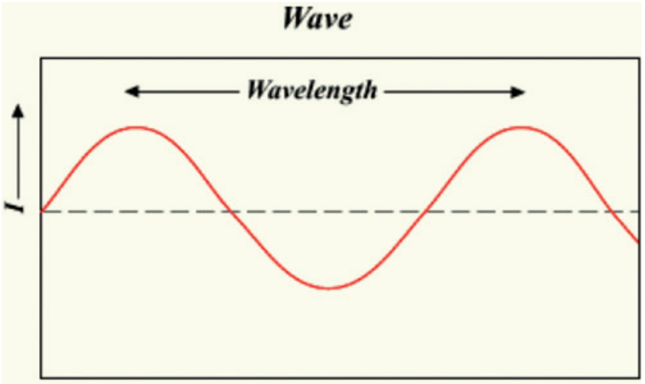

FIGURE 30.1 Wavelength is the distance between repeating points on a wave pattern.[15]

The principle behind laser technology is a quantum mechanical effect called *stimulated emission*, which was discovered by Einstein in 1917.[17] During stimulated emission, photons (discrete packets of light energy) are generated to produce a focused, coherent beam of light consisting of a single wavelength; in contrast, common light sources such as lightbulbs produce incoherent light, emitting photons in many directions over a wide spectrum of wavelengths (see Figure 30.1). For both types of light the amount of energy used is measured in joules (watts × sec) and the power (rate of energy use) is measured in watts (joules per second); however, a 40 watt laser will appear much brighter than a 40 watt lightbulb, for example. Another difference is that lasers can emit light either continuously or in pulses of higher peak powers, whereas regular light cannot be controlled in that way.[13]

A typical laser consists of three main parts: a laser medium, a pump source, and an optical resonator.[18] The wavelength a laser produces depends on the type and design of the medium and also on the alignment of mirrors in the optical resonator.

- The laser medium (also called gain medium) emits photons when excited; it can be a solid, liquid, or gas.
- The pump source provides energy that excites the lasing medium; it may be an electrical discharge, a flashlamp, or another laser.
- The optical resonator (also called optical cavity) is a mirror or system of mirrors that intensifies and amplifies light emitted from the medium; it does this by reflecting light back into the medium, sometimes several times, before it exits the laser.

TABLE 30.2 Lasers Used in Endovenous Laser Ablation of Varice

Diode lasers	
EVLT™ 	FDA Approval: 2002 Manufacturer: Diomed, Andover, MA Wavelength: 810 nm
Medilas D Compact Diode 	FDA Approval: 2003 Manufacturer: Dornier MedTech Laser GmbH, Germering, Germany Wavelength: 940 nm
ELVeS™ 	FDA Approval: 2002 Manufacturer: Biolitec, Inc., East Longmeadow, MA Wavelength: 810 nm, 980 nm
VenaCure™ 	FDA Approval: 2002 Manufacturer: AngioDynamics, Queensbury, NY Wavelength: 810 nm, 980 nm
Vari-Lase® 	FDA Approval: 2003 Manufacturer: Vascular Solutions, Minneapolis, MN Wavelength: 810 nm
Nd:YAG lasers	
CoolTouch CTEV™ 	FDA Approval: 2005 Manufacturer: CoolTouch, Roseville, CA Wavelength: 1320

LASERS USED IN EVLA

There are many types of lasers available, distinguished broadly by whether their medium is solid, liquid, or gas. The lasers used in EVLA (see Table 30.2) are all solid-state lasers of two types: diode and Nd:YAG.

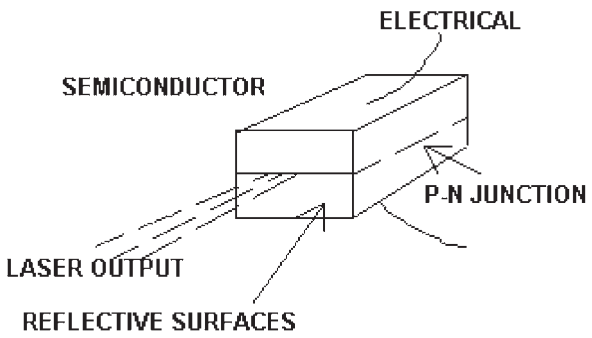

FIGURE 30.2 A diode laser uses a semiconductor and electrical current to produce a coherent light beam of a single wavelength. (Courtesy of Biolitec.)

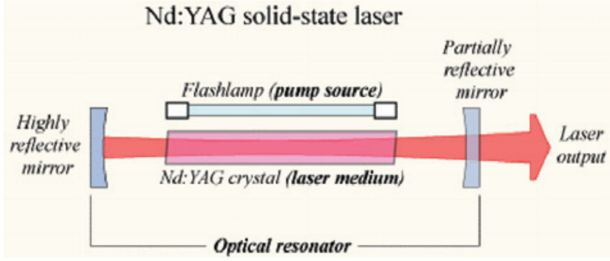

FIGURE 30.3 With Nd:YAG lasers, the medium is a solid crystal and the pumpsource is a flashlamp or other light source, such as a diode laser.[22]

Diode lasers (see Figure 30.2) are a common type of laser, such as you would find in your CD player or laser pointer, that use electrical current as their pump source. Their medium is a very thin, microscopic chip known as a semiconductor, which consists of two layered wafers of semiconducting crystals (e.g., silicon) cleaved at both ends with smooth parallel edges that act as mirrors.[19] The two wafers each have different electrical properties—one produces electrons and one produces the absence of electrons, known in solid-state physics as a *hole*.[20] Both wafers are extremely conductive, but the space between them, known as the p-n junction, is not. However, applying electrical voltage to the p-n junction can reduce the width of the junction, thereby making the exchange of electrons and holes possible and resulting in the emission of photons.[19,20] By manipulating the p-n junction, diode lasers allow electrical current to flow in one direction, but not the other.

Diode lasers have several advantages, including their high degree of electrical efficiency, compact and convenient construction, and high-speed operation; however, their output beams can be highly divergent and their peak energies are lower than what is required for some medical applications, although this last point can be overcome by tightly stacking together many small laser emitters. The diode lasers covered in this chapter have wavelengths of 810 nm, 940 nm, and 980 nm.

The other type of laser used in EVLA is the Nd:YAG laser (see Figure 30.3), the workhorse of solid-state lasers. Nd:YAG is an acronym for the medium used, a crystalline material called neodymium-doped yttrium aluminum garnet.[21] The medium is in the shape of a thin rod, which is flanked by a pair of mirrors. Rather than using electrical current as a pump source, Nd:YAG lasers are pumped by another light source, such as a diode laser or a flashlamp, and are able to build up and release energy to facilitate focusing on very small areas; however, they are larger, more complex to operate, and less electrically efficient than diode lasers. In this chapter the 1320-nm and 1064-nm Nd:YAG lasers will be discussed, although the 1064 nm normally is not used in the United States for EVLA.

EVLA MODE OF ACTION

The use of lasers to treat varicose veins is a relatively new application of laser technology, and the mode of action is not thoroughly understood. In general, the combination of intense thermal reaction and boiling blood is considered to be the mechanism of endovenous injury. During the procedure, the intravenously placed laser fiber emits infrared light that converts to heat, exceeding the boiling point of hemoglobin or water and boiling the blood.[8,23] The hot blood delivers extensive, thermal damage to the endothelium, which in turn becomes thrombotic and the vein occludes.[8] Although boiling bubbles and thrombosis are key in the EVLA mode of action, there appears to be no risk of embolism and a small risk of deep vein thrombosis (DVT) associated with the procedure.[8]

Each laser has a target molecule, known as a chromophore, that absorbs light of its particular wavelength (see Figure 30.4). The chromophore of 810-nm lasers is hemoglobin;[24,10] 940 nm and 980 nm lasers affect both hemoglobin and water;[24,10] and 1320 nm lasers target water alone.[25] To be effective, the lasers must be able to penetrate hemoglobin, water, or both to the point where sufficient energy is absorbed by the chromophore to generate a thermal reaction releasing steam bubbles.[10] Regardless of the type of laser, the intense thermal reaction and that boiling of blood is distributed along the inner vein wall.[10]

EVLA PROCEDURE

Although EVLA is applicable to refluxes of veins other than the GSV, treatment of this vein is particularly common; therefore, this chapter describes the procedure using the GSV as an example.[26] The surgical technique is similar for both diode and Nd:YAG lasers, with only slight modifications necessary when Nd:YAG lasers are used. Regardless

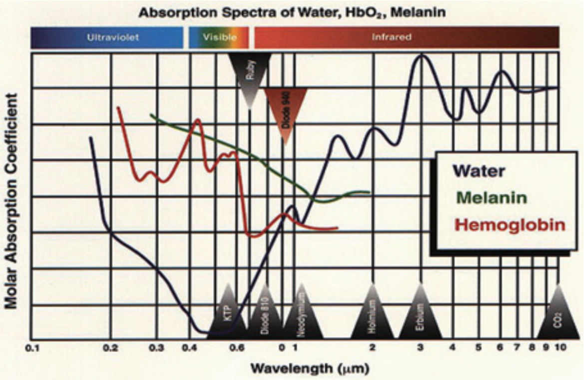

FIGURE 30.4 Light is absorbed by different chromophores depending on its wavelength. (Courtesy of Donier, MedTech, America Inc.)

FIGURE 30.5 A 4-French sheath is inserted into the GSV, just above the knee.

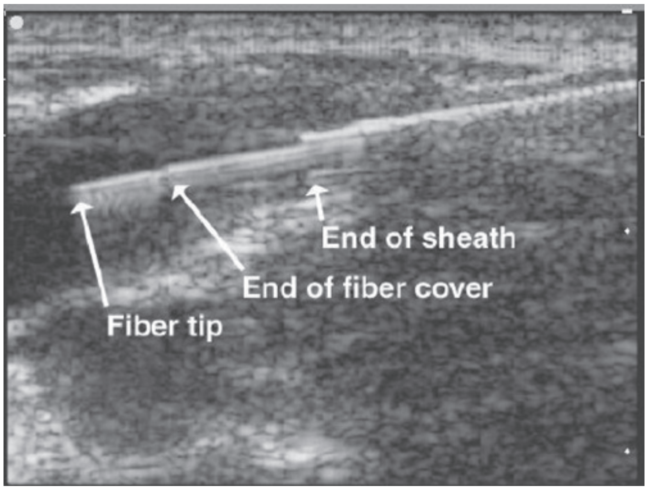

FIGURE 30.6 The tip of the fiber is visible using ultrasound.

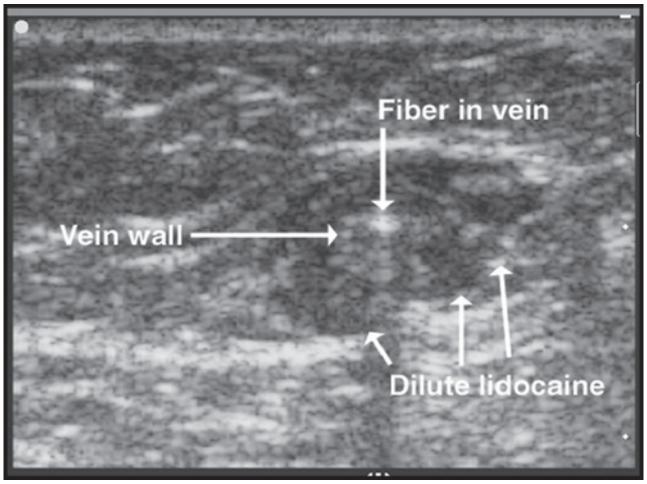

FIGURE 30.7 Tumescent anesthesia should place the vein to be treated approximately 10 mm from the skin and fill an area around the catheter that is approximately 10 mm in diameter.

of the laser, the procedure begins by the patient lying supine on a surgical table and being draped in the sterile mode. Local anesthetic is then administered to the skin to provide anesthesia.

Ultrasound-guided access to the GSV is then obtained, either at or below the knee, using a 21-gauge micropuncture catheterization set. A 5 F micro-sheath introducer is inserted into the GSV (see Figure 30.5). After removing the inner cannula from the micro-sheath, a .035-inch guidewire is advanced beyond the saphenofemoral junction (SFJ) into the common femoral vein, again under direct ultrasound guidance. A 45-cm or 65-cm 4- or 5-French sheath is then marked at the point of length of insertion, backloaded onto the guidewire, and advanced to 1.5 cm below the SFJ or just distal to the epigastric vein.

After the sheath is stabilized, the introducer and guidewire are removed and a 600-micron bare-tipped laser fiber is placed into the sheath. The laser fiber is then advanced to the end of the sheath by ultrasound guidance and the sheath is retracted. When using a diode laser, the sheath is retracted to the fiber's locking device and married, leaving the tip of the laser exposed; with the Nd:YAG 1320-nm laser, the sheath is retracted completely. Final laser position easily is determined by ultrasound (see Figure 30.6) and can also be verified directly because the skin becomes luminous where the laser tip, or aiming beam, emerges from the end of the sheath. The area around the entire venous segment being treated is then infused with dilute local anesthesia under ultrasound guidance; the infusion should create an ultrasound-verified 10-mm hypoechoic diameter around the vein and a sufficient amount of tumescent anesthesia to approximate a 10 mm distance from the skin to the vein (see Figure 30.7).

After the correct position of the laser is verified, laser energy is delivered at a determined wattage while the fiber is pulled back down the length of the vein. Laser manufac-

turers provide guidelines on the amount of power that should be used during EVLA; however, medical practitioners adjust the standards according to their professional experience and judgment. Laser energy can be emitted either continuously with constant, gentle pullback of the fiber, or in a pulsed mode with energy emitted only when the laser is held still, not when it is moving.[8] Pullback may be performed either by hand in the case of diode lasers or an automatic pullback machine in the case of Nd:YAG lasers. In either case, pullback rate is determined by the watts used and energy rate (joules/cm) required. With diode lasers, watts are set in the range of 10–14 and joules/cm are set in the range of 50–80; with Nd:YAG lasers, watts are between 5–7 and the energy rate is between 50–70 joules/cm (the automatic pullback device is usually set a 1 mm/sec). After the entire venous section has been treated with laser energy, the vein is then checked by ultrasound for closure and any abnormalities.

The puncture sight is covered with a sterile dressing and a full-thigh Class 2 compression stocking (30–40 mmHg) is placed on the leg. There is variation between physicians regarding how long the patient is told to wear the stocking; a suggested recommendation is to wear the stocking until the next evening and while awake for the next 7 to 10 days after that. The patient is also instructed to take ibuprofen for pain and to avoid high-impact aerobics.

EVLA CLINICAL OUTCOMES BASED ON LASER WAVELENGTH

Scientific studies on the safety and efficacy of EVLA are appearing more frequently in the literature, although to date there has been only one randomized, double-blind, prospective trial.[26] The literature that is available can be difficult to assess, since authors frequently use different measurements of outcome, and certainly the parameters of treatment vary between centers. In general authors look for complication and closure rates, although definitions of closure vary among trials from "no reflux" to "no flow verified by ultrasound." In addition, the physician must consider equally important symptom and quality-of-life outcomes,[4] which are both subjective and nonstandardized in the literature. Nonetheless, midterm clinical trial results are available and long-term experience is beginning to accumulate.

There is no scientific evidence that wavelength has any effect on long-term outcome (see Table 30.3), although in the short term differences can be found for some side effect rates. Clinical trial experience with the diode lasers has produced extremely low rates of DVT and paresthesia, apparently no skin burning, and no documented cases of pulmonary embolism;[7,27,28,29] both paresthesia and skin burns have been associated with 1064 nm laser treatment.[30] The most common side effects seen with all laser types are bruising, localized pain, induration and discomfort along the treated vein, and superficial phlebitis.

One trial has evaluated the parameters associated with successful occlusion at three-month follow-up.[31] Consecutive patients with incompetent GSV received EVLA using a 940-nm diode laser administered continuously with a pullback rate of 5–10 mm/second. Analysis showed that factors influencing whether veins remained closed at three months were higher laser fluence (J/cm^2), higher energy per vein length (J/cm), shorter distance from thrombus to SFJ at day 1 after EVLA, smaller proximal vein diameter, and longer total laser treatment time (see Table 30.4). Obviously outcome is also dependent on careful patient evaluation, treatment discussions, and long-term follow-up.[1]

810 nm VS 980 nm: A RECENT REPORT

To further determine whether EVLA outcomes are related to laser wavelengths, a randomized, double-blinded, prospective, single-center trial was undertaken in patients electing EVLA for GSV insufficiency.[26] Prior to treatment, patients completed an evaluation of limb pain, rated on a scale of 1 to 5, where 1 was "no pain" and 5 was "intense pain"; patients also completed an evaluation of the physical and emotional impact of their leg problems on their daily living.

Fifty-one patients underwent the procedure as described earlier in this chapter; 30 limbs were treated with a 810-nm laser and 30 with a 980-nm laser. Immediately following the procedure and again at 72 hours the treated vessels were confirmed closed using duplex ultrasound. At 72 hours, three weeks, and four months patients completed a survey of physical activity and underwent an examination of symptoms.

No differences in outcome or in any physical activity or symptom survey items were apparent at 72 hours following the procedure. As follow-up continued, patients in the 810-nm group experienced more bruising at one week (P = 0.007) and worse pain intensity (P = 0.028) and varicose vein ratings (i.e., visible varices) (P = 0.004) at four months, but significantly less itching at three weeks (P = 0.031). Ten patients in the 810-nm group and three patients in the 980-nm group experienced phlebitis of the treated vein, which was directly related to increased postprocedural pain. At one year, two legs in each group exhibited reflux by duplex ultrasound using the compression and release method, indicative of returned flow in the GSV. All other limbs remained free of flow at their one-year follow-up, for a success rate of 93%.

This trial shows that both the 810-nm and the 980-nm lasers are effective with no complications or adverse events. Although there was a short-term trend in favor of the 980-nm laser, those differences did not lead to the need for

TABLE 30.3 EVLA Outcomes by Laser Wavelength

Author, year	Design of trial	Veins treated (patients)	Diameter of pretreatment vein, mm range (mean)	Parameters	Follow-up	Complete occlusion rate % (patients/n)	Side effects
				810 nm Wavelength			
Min, 2001[7]	Prospective, nonrandomized, consecutive enrollment multicenter	90 GSV (84)	3–27 (11)	10–12 W, pulse duration 0.8–1.0 seconds	1 week 1–9 months (6 months, mean)	97 (87/90) 99 (89/90)	Self-limiting bruising, mild discomfort, soreness along GSV, paresthesia in one patient
Min, 2003[32]	Prospective, nonrandomized consecutive enrollment single center	499 (423)	4.4–29 (11)	55% of limbs treated with 14 W continuous mode, mean delivery of laser energy 123 sec, 1727 J	1 month 6 months 1 year 2 years	98 (490/499) 99 (390/396) 98 (310/318) 93 (113/121)	Bruising, tightness or pulling along GSV, superficial phlebitis of varicose tributaries
Min, 2004[33]	Prospective, nonrandomized consecutive enrollment single center	1000 (925); 811 GSV, 80 SSV, 96 AASV, 13 PASV	4.1–38 (10)	14 W continuous mode, 100% success if treated with >70 J	<1 year >3 years	96 (309/322) 99 (218/219)	Bruising and mild tenderness
				940 Wavelength			
Proebstle 2002[34]	Prospective, consecutive enrollment	109 GSV (85)	Not available	15 J administered in 1 second pulses	1 year	90 (94/104)	Pain and induration along the vein, symptoms of thrombophlebitis
Proebstle 2002[8]	Patients selected from phlebology clinic	31 (26)	4.0–9.9 (6)	15 W, pulsed (1 second on, 2 seconds off)	28 days	97 (30/31)	Moderate bruising, slight-to-moderate local pain, induration along the vein
Proebstle, 2003[28]	Patients selected from phlebology clinic	41 (33) intended; 39 (31) completed	2.0–6.0 (3.4)	15 W continuous pullback 0.5–1 cm/sec; or 15 J with 1-second pulses	1 day 6 months, median	100 (39/39) 100 (37/37)	Pain, bruising, induration, paresthesia, periphlebitis, DVT in one patient
				980 nm Wavelength			
Kabnick, 2002[35]	Patients with GSV reflux confirmed by duplex ultrasound	20 GSV (15)	Not available	12 W, pullback rate 10–12 cm/min	Immediate	100 (20/20)	Bruising, discomfort or pain, superficial phlebitis
Oh, 2003[9]	Patients of phlebology clinic chose either traditional surgery or EVLA	15 GSV (12)	Not available	10–12 W in pulsed fashion with 1–2 seconds	1, 4, and 12 weeks	100 (15/15)	Bruising, mild tenderness, induration, superficial thrombophlebitis in one patient
Kabnick, 2004[29]	International Registry	7611 limbs, 7061 GSV	Not available	Not available	Not available	96	Bruising, paresthesia, burns 0.5%, DVT 0.3%

TABLE 30.3 (*continued*)

Author, year	Design of trial	Veins treated (patients)	Diameter of pretreatment vein, mm range (mean)	Parameters	Follow-up	Complete occlusion rate % (patients/n)	Side effects
			810 nm Vs 980 nm Wavelength				
Kabnick, 2005[26]	Randomized, double-blind, single-center	810 nm laser: 30 GSV	Not available	10 W, continuous pullback at 50 joules/cm	1 year	810 laser: 93 (28/30)	Phlebitis, pain, bruising, itching
		980 nm laser: 30 GSV			1 year	980 laser: 93 (28/30)	
			1064 nm				
Chang, 2002[30]	Not available	252 (149)	Not available	10–15 W, 10-second pulse duration	1–2 years (19 months, mean)	97 (244/252)	Local paresthesia, bruising, lower-limb swelling, dyschromia, superficial burns and phlebitis, hematomas
				1320			
Goldman, 2004[2]	Prospective, consecutive	24 GSV (22)	0.5–1.2	5 W, 1 mm/second automatic pullback	6–12 months (8 months, mean)	100	No pain or phlebitis, bruising not mentioned

W = watts; J = joules; GSV = Great Saphenous vein; SSV = Small Saphenous vein; AASV = anterior accessory saphenous vein; PASV = posterior accessory saphenous vein; LSV = lesser saphenous vein

TABLE 30.4 Parameters and EVLA Outcome at Three Months Using a 940-nm Laser[31]

Parameter	Median value of parameter: Closed veins	Open veins	*P* value
Laser fluence (J/cm^2)	13.2	7.2	<.001
Energy per vein length (J/cm)	23.8	19.3	.004
Distance thrombus to SFJ at day 1 after EVLA (cm)	1.1	2.5	.004
Proximal vein diameter (cm)	0.64	0.90	.002
Total laser time (seconds)	91.0	72.3	.046

TABLE 30.5 Significant Differences between 810 nm and 980 nm Outcomes in EVLA[26]

Outcome parameter	810 nm Mean (n)	980 nm Mean (n)	*P* value
Bruising at 1 week*	2.4 (30)	1.55 (3)	.0047
Itching at 3 weeks†	0.167 (30)	0.50 (30)	.031
Pain intensity at 4 months†	1.5 (30)	1.21 (30)	.028
Varicose vein rating at 4 months†	.97 (30)	.31 (30)	.004
Phlebitis	10 (30)	3 (29)	.08

*Based on a 5-point scale, where 0 = no visible bruising and 5 = extreme bruising.

†Based on a 4-point scale ranging from absent to severe.

additional treatment or to any difference in long-term outcomes between the two treatment groups. This study confirms earlier published reports showing few complications associated with the 810-nm and the 980-nm lasers in EVLA.

ONGOING RESEARCH BY THE AUTHOR

A clinical trial is under way comparing EVLA using 980-nm or 1320-nm lasers and RF ablation. To date, no trial has adequately compared these three treatment methods, although discussion abounds as to the advantages and drawbacks of each. The trial is a randomized, double-blind, prospective trial with methods similar to the trial described earlier; it is expected that results may help further differentiate these noninvasive treatment methods for varices.

CONCLUSION

Although clinical trial experience is limited and there is no standardized system for evaluating EVLA outcomes, it is clearly effective and safe in the treatment of varices (see Table 30.5). There is no scientific evidence demonstrating superior long-term results using one laser wavelength over

another, although subtle short-term differences in postprocedural bruising, pain, itching, and phlebitis have been noted; however, none of these differences is lasting or appears to impact vein occlusion rates. More double-blinded, randomized, prospective trials may be necessary to provide further insight into the importance of the many variables in EVLA therapy; however, at this time it appears that the lasers used for ablation of the saphenous veins are effective with minimal morbidity and complications.

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CHAPTER

31

VNUS Closure of the Saphenous Vein

NICK MORRISON

INTRODUCTION

Lower extremity varicose vein disease is associated most often with truncal venous insufficiency involving the saphenous system; the Great Saphenous vein, the Small Saphenous vein, and/or incompetent perforator or tributary veins. Management of this disease process historically has been treated with groin-to-ankle stripping of the Great Saphenous vein with complete interruption of the tributaries near the saphenofemoral junction.[1] More recent reports of invagination stripping (PIN) of the Great Saphenous vein from groin to knee demonstrate comparable results, with less tissue damage, faster and less painful recovery, and better cosmetic results than the classic stripping procedure.[2]

Since 2000, radiofrequency endovenous ablation has been reported to be a safe and effective method of removing the proximal portion of the Great Saphenous vein from the venous circulation, with faster recovery and better cosmetic results than either the classic or PIN stripping procedures.[3] The Closure® procedure, using a radiofrequency (RF) catheter and generator (VNUS Medical Technologies, Inc, Sunnyvale, California), delivers electromagnetic energy to destroy the target vein *in situ*. Extensive international experience with this technique has resulted in its rapid adoption by phlebologists. As a result of this experience with treatment of the Great Saphenous vein, successful ablation of the Small Saphenous vein, major tributaries, and even perforator veins has been reported.[4] As with a stripping procedure, it is important to treat the distal Great Saphenous vein and incompetent tributary and perforator veins in order to eliminate all major sources of venous insufficiency.[5]

RF Literature

Following extensive animal and clinical investigation,[6] clinical trials using RF energy for ablation of the Great Saphenous vein have demonstrated excellent success rates, comparable to or better than historical results following stripping.[3] A prospective randomized study directly comparing RF ablation with stripping, reported by Lurie et al., confirmed these findings.[7] An earlier report from 2000,[15] and follow-up reports as long as five years post RF ablation[4] confirm the safety and efficacy of this method of saphenous vein ablation. Successful ablation rates of nearly 90% or more routinely are demonstrated,[9,10] although one center in the United Kingdom has reported an unprecedented 100% success rate with few complications.[11]

Complications following RF ablation include deep vein thrombosis (DVT), paresthesia, pain, bruising, leg edema, localized thermal skin injury, hematoma, and superficial thrombophlebitis. The most serious of these, DVT, generally is reported to be less than 1%, but has been reported as high as 20% in one small group of patients.[12] Paresthesia, reported from 2 to 16%, is usually transitory. The rates of the other reported complications are low.[13]

TECHNICAL EQUIPMENT

RF Generator

The generator produces and delivers radiofrequency energy via a catheter into the vein wall by contact with retractable electrodes at the end of the catheter, causing resistive heating of the vein wall sufficient to denude the endothelium and denature and shrink the intramural

collagen. Such tissue damage results in fibrotic occlusion of the target vein, in addition to an inflammatory response that enhances vein wall destruction. Heat is produced when the RF energy causes excitement of the molecules of the vein wall as it is transmitted from the catheter, into the vein wall, and back into the central electrode of the catheter. Thus, it is the impedence in the vein wall to the passage of the RF energy that causes heat destruction, much like light energy is produced by the passage of electricity through the filaments of a lightbulb. A micro-thermocouple mounted on one of the electrodes continuously measures vein wall temperature and provides feedback to the microprocessor in the generator. By limiting the temperature to 85 to 90 degrees Celsius, boiling, vaporization, and carbonization of the tissues is avoided. In addition, power output and impedence are also continually monitored to be sure the RF energy is being effectively delivered to the vein wall. The generator will automatically shut down if the impedence is so high as to prevent adequate transmission of RF energy into the vein wall. The heat generated has been shown to penetrate 1 mm in tissue, and in the absence of dilute local anesthetic surrounding the Great Saphenous vein, heating of surrounding tissues can occur by means of conduction. The addition of the local anesthetic mitigates damage to the surrounding tissue by conducted heat. The face of the generator displays elapsed treatment time, vein wall temperature, impedance (in ohms), and power output, allowing continuous monitoring of several parameters to accomplish successful ablation of the target vein.

RF Catheter

The catheter, with retractable electrodes to transmit the radiofrequency energy, is available in two sizes: 6 Fr and 8 Fr. Early in the RF experience, treatment of veins larger than 12 mm diameter was not recommended. However, studies in several centers have demonstrated that given adequate ultrasound-guided deposition of dilute local anesthetic completely surrounding the target vein, successful treatment of veins much larger than 12 mm is quite feasible.[8] Both catheters also have a central lumen that allows for passage of fluid (often heparinized saline) or a guidewire to assist advancement of the catheter to the uppermost limit of the intended treatment.

Pathologic/Physiologic Effects of Radiofrequency Energy

In his text, *Vein Diagnosis and Treatment*, Weiss reported the use of caprine models to evaluate the physiologic and pathologic changes following RF ablation of the great saphenous vein.[6] Ultrasonographic changes demonstrated by duplex were occlusion in 100% of veins, and decreased mean diameter from 5 mm to 1 mm. Acute histologic changes include "endothelial denudation, thrombus formation, thickened vein walls, denaturation of tissue with loss of collagen vessel walls, and neutrophil inflammation." After six weeks, abundant new collagen with fibrosis of the vein wall and encroachment on the vein lumen was seen.

Clinical Experience

Numerous reports by Chandler,[15] Pichot,[9] Perrin,[17] Goldman,[13] Bergan,[14] Weiss,[10] and Kistner[3] have shown the RF ablation procedure to be a safe and effective means of removing the Great Saphenous vein from the venous system, with excellent early and mid-term results.

Recently published five-year data from the VNUS registry suggest that the Closure® procedure is effective in occluding saphenous veins and abolishing reflux.[4] In this report, patients (22% male and 78% female) with symptomatic saphenous reflux and a mean saphenous vein diameter of 7.5 mm, and a maximum of 24 mm, were enrolled in the registry. Mean age was 47.4 years. Eighty-nine percent of treated veins were Great Saphenous veins above the knee, 4.1% the entire Great Saphenous vein, and 5.6% were Small Saphenous and accessory saphenous veins. Vein occlusion at one year was documented by duplex ultrasound in 87.1% of legs; 88.2% at two years, 83.5% at three years, 84.9% at four years, and 87.2% at five years. Major refluxing tributaries required additional treatment, such as sclerotherapy or ambulatory phlebectomy.

In a prospective, randomized study reported by Lurie et al., the RF ablation procedure was compared to the conventional high ligation/stripping procedure with respect to short-term recovery and cost. Shorter convalescence, less postoperative pain, and lower overall economic costs were demonstrated with RF versus surgical ablation.[7]

PROCEDURE

Patient Selection

Inclusion criteria should include symptoms and physical signs of venous insufficiency, duplex scan showing a patent proximal vein with reflux greater than 0.5 seconds, patent deep venous system, vein conducive to catheterization (dependent on the experience of the operator), and fully mobile patients. Absolute exclusion criteria will include arteriovenous malformations, restricted ambulation, and deep venous obstruction. Relative exclusion criteria will include vein tortuosity, veins less than 2 mm or greater than 25 mm, partial obstruction of the proximal vein, and known thrombophilia.

Technique

Many practitioners have preferred to perform these procedures in the hospital surgical or radiological suites. Recently, a variety of factors have combined to encourage displacement of the endovenous ablation procedure from the hospital and into the office setting. Furthermore, although the ablation procedure often is performed on veins other than the Great Saphenous vein, the technical details remain quite similar. The following description of the procedure for the great saphenous vein is given with this in mind.

After obtaining informed consent, patients may be given an oral or intravenous sedative prior to the procedure. The patient is placed on an adjustable operating table (with Trendelenburg capability), and the course of the Great Saphenous vein, from the saphenofemoral junction to the insertion site, is mapped and marked with an indelible marker. The insertion site is chosen to maximize treatment length and to assure facile access.

The portion of the Great Saphenous vein below the knee is not routinely treated with RF endovenous ablation because of the increased risk of paresthesia from damage to the saphenous nerve, which is in close proximity to the vein below the knee. Access to the Great Saphenous vein may be made using an ultrasound-guided, percutaneously placed needle, or via microincision and hooking of the Great Saphenous vein for direct venipuncture. If the percutaneous method is used, Nitropaste may be applied to the proposed insertion site prior to the sterile surgical prep to improve access by dilating the vein and preventing venospasm. It is sometimes appropriate to choose a primary access site and a higher, larger diameter, secondary (backup) access site in case access at the primary site is unsuccessful. Perivenous or intramural hematoma from unsuccessful attempts at cannulation may render that portion of the Great Saphenous vein technically inaccessible leading to the need for a secondary site. As the practitioner's ultrasound-guided technical skills improve, even Great Saphenous veins as small as 2 mm in diameter or less, or more than 25 mm in diameter, can be cannulated successfully.

The first attempt at cannulation of the Great Saphenous vein is the most likely to be successful, so the insertion site should be chosen carefully to make access as ergonomically feasible as possible. Just below the knee, the Great Saphenous vein is relatively anterior. And with the patient's operative leg externally rotated, this site becomes more advantageous than in the distal or mid thigh. And even though the saphenous nerve is closer to the vein in this area, the RF catheter sheath will prevent treatment of this portion of vein, and thus limit the possibility of nerve damage.

Following removal of the Nitropaste, the leg is cleansed, groin-to-insertion site, with an antiseptic. The operative area is isolated with sterile drapes. After infiltration of local anesthetic at the insertion site, an introducer needle is inserted into the Great Saphenous vein under ultrasound guidance; or a small incision is made and the vein is elevated through the skin incision with a phlebectomy hook. After advancement of a guidewire into the vein, a 5 cm sheath is advanced into the vein, and the RF catheter is then advanced to near the saphenofemoral junction, just below the entrance of the superficial epigastric vein into the Great Saphenous vein, confirmed by ultrasound. Occasionally, passage of the RF catheter may be impeded by vein tortuosity. Usually straightening of the leg or manipulation of the catheter by external compression, or shifting of the thigh will allow advancement of the catheter. Segmental stenosis from previous sclerotherapy also will impede advancement of the catherter. In this case, or if the vein is so tortuous as to not allow passage of the catheter, a second cannulation, with another insertion kit, will allow treatment of first the proximal and then the distal segments of the Great Saphenous vein.

Ultrasound-guided high volume, dilute anesthesia (.1–.25% Xylocaine with epinephrine/bicarbonate) is then injected into the saphenous compartment (see Figure 31.1) from the insertion site up to 3 cm below the saphenofemoral junction. (Alternatively, higher volume dilute anesthetic can be injected into the entire thigh generally surrounding the vein, without the need for ultrasound guidance). The patient is placed in a moderate Trendelenburg position and the final position of the tip of the RF catheter confirmed by ultrasound (see Figure 31.2). The anesthetic solution is injected into the tissue surrounding the proximal 3 to 4 cm of the Great Saphenous vein. External hand compression may be applied to the leg over the tip of the catheter as it is withdrawn. Early in the RF experience, an Esmarck bandage was used for external compression. However, infiltration of the local anesthetic directly into the saphenous sheath under

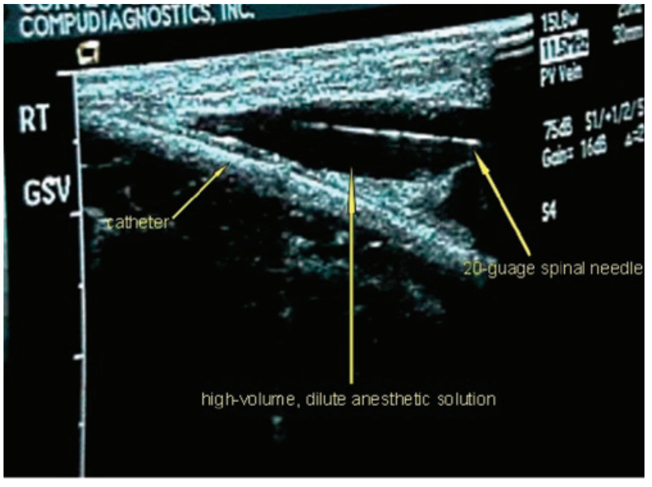

FIGURE 31.1 Great Saphenous vein, with catheter inside, compressed by local anesthetic solution.

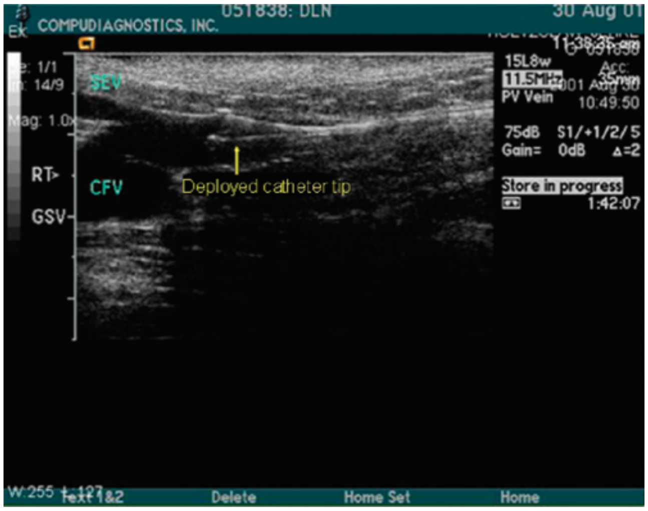

FIGURE 31.2 SEV = superficial epigastric vein, CFV = common femoral vein.

TABLE 31.1 Intraoperative Adverse Events

Technical challenges	Adverse patient events
Difficult access	Painful insertion
Trouble threading introducer wire/catheter	Dysrhythmia
Treatment interruption	Vagal reaction
Unable to reinsert catheter	Transient heat
GSV tortuosity	Saphenous nerve pain
Aneurysmal segments	

TABLE 31.2 Postoperative Adverse Events (or Expected Sequelae)

Bruising	Paresthesia
Skin burn	Superficial thrombophlebitis
Lymphedema	Deep vein thombosis
Infection	Intramural hematoma

ultrasound guidance has largely obviated the need for this cumbersome step.

The withdrawal rate for the RF catheter is adjusted to maintain the temperature of the tip at 85 to 90ºC. As the RF catheter is withdrawn from the distal portion of the treated segment into the sheath, the impedance will rise rapidly, and the generator will automatically shut down. On conclusion of the procedure, Doppler confirmation of the patency of the common femoral artery and vein, as well as successful occlusion of the great saphenous vein with a residual diameter less than 2 mm are recorded. Patients may then be placed in compression therapy, for example, short-stretch bandages, and 30–40 mm Hg compression hose (thigh-high or panty—patient's preference). Compression should be maintained for at least several days, if not longer, to enhance successful ablation. Adjunctive saphenofemoral junction ligation is not necessary.

Follow-up

Because of the possibility of incomplete ablation or recurrent patency of the treated vein, and the need for adjunctive treatment of the distal Great Saphenous vein, the refluxing tributaries, and/or Small Saphenous vein, color-flow Doppler ultrasound, interviews, and physical examinations at appropriate intervals are needed to assure a successful outcome. At a minimum, patients should be examined at one week, six months, and one year following RF ablation of the Great Saphenous vein. More frequent follow-up visits often will reveal the need for adjunctive treatment earlier in the postoperative course, and result in more complete treatment of the patient's venous insufficiency with better resolution of the patient's symptom complex. It is simply not appropriate to merely ablate the proximal Great Saphenous vein, and expect the patient's symptoms and varicosities to resolve. Unless one is committed to a program of meticulous follow-up and adjunctive treatment, the practitioner and the patient will be left with unsatisfactory results.

Complications

Complications are divided into intraoperative and postoperative adverse events.

Intraoperative adverse events can be divided into technical challenges and adverse patient events (see Table 31.1). The technical challenges one may encounter are difficult access (venospasm, access location), problems threading the catheter (vein tortuosity, aneurysmal segments, or sclerosis from previous sclerotherapy), and treatment interruption (generator shutdown secondary to high impedence because of coagulum build-up on the tip of the catheter. This will require removal of the catheter and cleansing of the tip in order to restore the flow of radiofrequency energy). Adverse patient events that can occur are dysrhythmia or vagal reaction (often because of anxiety) and saphenous nerve pain or transient heat (inadequate anesthetic infiltration).

Postoperative adverse events (or expected sequelae) include bruising, paresthesia, infection, intramural hematoma, skin burn, superficial thrombophlebitis, lymphedema, and deep vein thrombosis (see Table 31.2). Bruising is nearly always minimal, and of less than two-week duration. Unlike following groin-to-ankle stripping, paresthesia following endovenous ablation is usually mild, short-lived, and limited to the distal thigh. It is seen in 1 to 16% of patients, and its rate of occurrence is inversely related to the experience of the practioner with ultrasound-guided techniques. Infection, intramural hematoma, and skin burns are rare, occurring in less than .1% of patients. These are avoided

with adequate sterile technique. Infection is avoided with good sterile technique, while the ultrasound guided anesthetic, in ample quantities, will serve to protect the structures in close proximity to the vein from thermal injury, including the overlying skin. Superficial thrombophlebitis is seen in less than 10% of cases, and responds to the usual clinical measures of anti-inflammatory medication, compression, and ambulation. Lymphedema has not been reported, but we have seen it in our own center, and is believed to be caused from unrecognized impaired lymphatic drainage usually present prior to any procedures. Treatment of this complication (or more likely sequela) will entail therapeutic lymphatic massage, compression with multilayered low-stretch bandages and compression hose, and exercise.

Deep vein thrombosis is the most significant complication and is generally reported to occur in less than 1% of the patients (depending on the duplex scanning interval and the quality of the examination). Most reported cases are calf vein thrombosis, and of limited clinical significance. More proximal thromboses do occur, however, and should be aggressively searched for and treated. Therapy is usually as an outpatient, with compression, ambulation, anti-inflammatory medication or anticoagulation (short term with low molecular-weight heparin, or longer term with oral agents), and even percutaneous thrombolytic/thrombectomy therapy for more proximal thromboses.

One complication, of great interest because of its relative absence, is neovascularization. Neovascularization commonly is seen following the traditional surgical high ligation procedure, wherein all tributaries of the great saphenous vein are carefully dissected and divided.[18] This is thought to be secondary to "frustrated" venous drainage from the abdominal wall and perineum. The ultrasound picture of neovascularization, seen as grape-like clusters of veins in the groin, is quite characteristic (see Figure 31.3). Whether this is actually the development of new veins, or simply enlargement of previously existing veins, the result is recurrent reflux down veins in the thigh and lower leg. The endovenous ablation procedure deliberately leaves the superficial epigastric vein intact, which, it is believed, has resulted in few reports of neovascularization at the five-year interval, or of thrombus extension from the Great Saphenous vein into the common femoral vein.

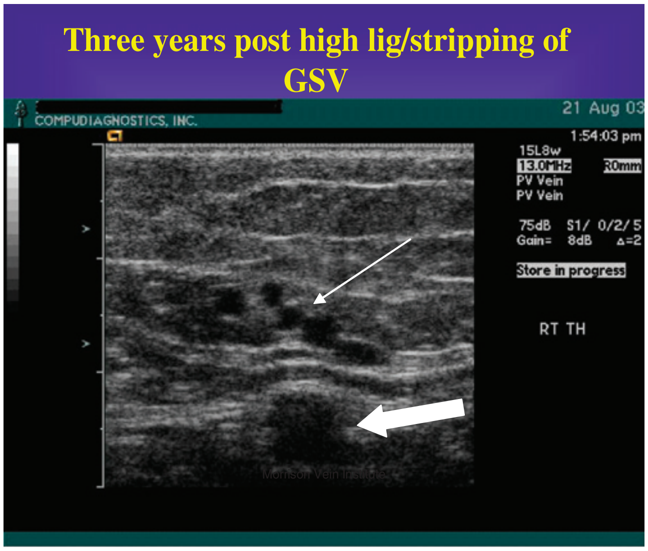

FIGURE 31.3 Block arrow: common femoral vein; Line arrow: neovascularization.

DISCUSSION

Considerable confusion in the literature has emerged regarding the definition of successful treatment, the means used to detect treatment failures, and the reporting of results. Agreement on the very definition of success has not yet been achieved, being variably reported as sonographic absence of the target vein,[8] no flow in treated segment,[19] absence of visible reflux,[9] segmental patency of no more than 5 cm without reflux,[16] and resolution of symptoms.[19] Extensive advancements in the technology of ultrasound over the past ten years have allowed far more critical evaluation of clinical results than were possible in the past. As a result of these advancements, it is now possible to more readily identify incompletely ablated veins. Recurrent patency can occur anywhere in the RF-ablated portion of the vein, either along its length or segmentally. Segmental recurrent patency usually is seen at the site of an incompetent perforator or a refluxing tributary. And because there is likely to be closed segments above and/or below the patent segment, distal compression of the closed portion of the vein to identify reflux is futile. Likewise, using Valsalva's maneuver to identify proximal patency is unreliable and lacks reproducibility. More sensitive and critical ultrasound examination of treated veins brings into question earlier reports in which success is defined as "absence of visible reflux" or "resolution of symptoms." Indeed, many patients will experience temporary resolution of symptoms following an ablation procedure, only to have those symptoms return when reflux becomes clinically significant, generally within a few months' time.

Identification of recurrent patency, incomplete ablation, or treatment failures is very dependent on the sensitivity of the ultrasound equipment used for postoperative examination, the expertise of the sonographer, and the vigor with which the examination is conducted. In a study of ultrasound equipment, from our center, reported at the UIP meeting in 2003, five different ultrasound machines commonly used in vascular laboratories were evaluated. Six patients with moderate reflux were examined by the same registered vascular technologist, using all five machines. The sensitivity of each machine was found to be 100% (for the control machine),

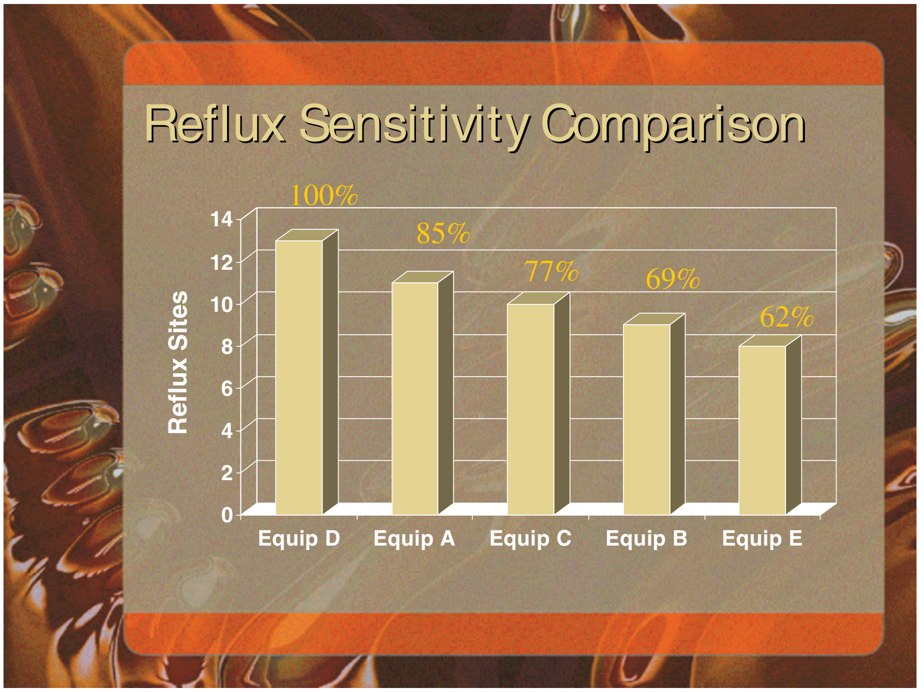

FIGURE 31.4 Comparison of sensitivity of duplex equipment.

and 85%, 77%, 69%, and 62% for the other four machines (see Figure 31.4). In other words, reflux was *not* identified in 15%, 23%, 31%, and 38% of the veins known to have reflux. Since identification of flow is directly related to the sensitivity of the duplex machine, it is reasonable to assume that following patients for postoperative results will be greatly influenced by the equipment utilized for the examinations. Further, the expertise of the sonographer, whether they have extensive superficial venous experience, and how carefully the examination is carried out are all factors of paramount importance in critical reporting of results.

Additionally, no consensus has been established on such critical reporting issues as duration of follow-up and duplex scanning intervals, quality and sensitivity of duplex equipment used for follow-up examination of a treated vein, and training and experience of the duplex operator.

Duplex examination for successful ablation of a vein should include gray scale, compression, and color flow Doppler in order to be complete. However, patients often have ultrasound-guided foam sclerotherapy for distal segments of the treated vein, refluxing tributaries of the treated vein, and incompetent perforators. Such foam sclerotherapy has had an unexpected effect on critical analysis of successful ablation. Since foam is an excellent contrast medium with ultrasound, injection of foam into distal vein segments, tributaries, and incompetent perforators has been very revealing in following post-ablation patients. The ablated vein, which remains sonographically identifiable, but by all duplex ultrasound criteria is completely occluded, commonly is found to have foam within the vein following injection of a tributary, perforator, or distal segment. This further calls into question even the most critical examination techniques. Whether these minimally patent segments will become clinically significant is unanswered at this time. But certainly patients who complain of localized pain in the area of a previously ablated vein deserve very careful examination to identify the incompletely ablated segment.

In our own center it has become apparent that most patients require additional treatment in order to remove all sources of insufficiency from the venous circulation. Adjunctive treatment may include such things as endovenous ablation of the incompetent Small Saphenous vein, accessory saphenous or major saphenous tributaries, and/or incompetent perforators; ambulatory phlebectomy (or powered phlebectomy); ultrasound-guided sclerotherapy (foam or liquid); and visual sclerotherapy. These techniques will help to achieve the greatest resolution of the patient's varicosities and symptoms. Much like high surgical ligation of major tributaries with avulsion phlebectomy distally, and ligation and/or stripping of the Small Saphenous vein completes the conventional surgical treatment of high ligation and groin-to-knee or ankle stripping of the Great Saphenous vein, these minimally invasive methods following endovenous ablation procedures allow more complete treatment of the patient's venous insufficiency disease.

In our experience of nearly 2000 endovenous ablation procedures, several important issues have come to light. For example, any ablated vein segment that remains sonograph-

ically visible one year post treatment must still be at least partially patent. The most effective way to prove recurrent patency of a segment, and treat it at the same time, is to search for a perforator or tributary in the area of the visible segment, and inject foamed sclerosant, under ultrasound guidance, into the perforator or tributary. The foam will be seen to course into the visible segment, confirming its patency, in spite of a negative examination for flow. Because incomplete ablation is treated when it is identified, it is unclear if, or how many of, these partially patent segments would have closed without adjunctive ultrasound-guided foam sclerotherapy. However, a number of patients who were found to have recurrent patency, and who were unwilling to have follow-up ultrasound-guided foam sclerotherapy, have been followed. Over time, most of these patients have developed recurrent symptoms or signs of venous insufficiency.

Factors we found to be associated with incomplete ablation were preoperative deep venous reflux and sites of major tributaries or perforators. Factors found *not* to be associated with incomplete ablation were large or aneurysmal segments and patient age.

It has been reported that most incompletely ablated veins will be seen in the first few months following treatment, since failure rates do not steadily increase over time.[4] However, we have identified patients more than three years following apparently successful ablation, with recurrent symptoms and partially patent segments. Thus, it is necessary to perform thorough follow-up of these patients for one year, and then either yearly or certainly when recurrent symptoms occur.

The cost of performing the procedure in the office setting under local anesthesia, exclusive of the provider's time, is generally about $1100.

CONCLUSION

Radiofrequency endovenous ablation is generally safe. Technical challenges, intraoperative and postoperative adverse events, and sequelae are infrequent and generally are seen less frequently than with more traditional surgical procedures.

Differences in methods of follow-up examination, and in definitions of successful ablation, may help explain differences in results between published reports and in those seen in the providers' own clinical setting. Only long-term follow-up will show where these minimally invasive methods belong in the therapeutic armamentarium of the treatment of chronic venous insufficiency of the lower extremity. Although some surgeons have expressed the view that none of these techniques has yet been shown to better conventional surgery in the long term,[20] the patient's perception uniformly has been that minimal invasion is better.

ADDENDUM

Technical Considerations

With respect to treatment of aneurysmal segments of the GSV, high-volume, dilute anesthetic solution, accurately placed into the saphenous compartment under ultrasound guidance, is critical to successful treatment. Very large GSVs, up to 35 mm, have been ablated successfully with the RF procedure. It is apparent that well-placed anesthetic solution is the single most important factor in successfully treating GSV incompetence with an ablation procedure. As these procedures have been performed in the office setting, under local anesthesia, with minimal oral sedation, it is clear that well-placed anesthetic solution is also important for the elimination of the sensation of transient heat felt by the patient.

Percutaneous, ultrasound-guided access to even very small GSVs can be achieved, and access times will diminish quickly and dramatically with experience.

Intramural hematoma at the SFJ has not been previously described, and after deducing and eliminating inadvertent SFJ wall puncture during injection of the local anesthetic, with resultant intramural hematoma, it was not seen again in this center.

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CHAPTER

32

Treatment of Small Saphenous Vein Reflux

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There are more variations of anatomy and pathophysiology for small saphenous reflux than at any other site, and these will be illustrated by findings from duplex ultrasound scanning. There appears to be no consensus as to best treatment for small saphenous reflux, in part due to lack of objective information regarding outcome. What information is available shows poor results from traditional treatment by surgery, persuading us to recommend that endovenous techniques be considered.

SURGICAL ANATOMY

The anatomy of veins in the popliteal fossa is highly variable, unlike the anatomy at the saphenofemoral junction, which is relatively constant. This section will highlight only findings relevant to choice and execution of treatment for Small Saphenous Vein reflux.

The Small Saphenous Vein (SSV) is always present and frequently continues as the thigh extension (TE), but there is a variable connection of the SSV with the deep veins and a variable termination of the TE. These patterns were well described by Giacomini in 1873[1] and have now been clearly defined by ultrasound.[2–8]

Small Saphenous Vein (SSV)

The SSV passes up the back of calf in the midline between the bellies of the gastrocnemius. It is distinguished from tributaries on ultrasound by the observation that it lies in a fascial compartment throughout its entire length just as for the Great Saphenous Vein (GSV).[8] It turns deep to join the popliteal or femoral vein at the saphenopopliteal junction (SPJ) in approximately 75% of limbs.[2] The gastrocnemius veins join the SSV rather than the popliteal vein at or near the SPJ in up to one-third of limbs.[6]

The sural nerve lies just lateral to the SSV but not with a common association of the perivenous and perineural fasciae as frequently occurs with the GSV and saphenous nerve.[9] The common peroneal and posterior tibial nerves are adjacent to the terminal SSV particularly if there is a high SPJ, with a variable relation lying on either side or even entwining with the vein.

Thigh Extension (TE) and Vein of Giacomini

The embryological pathway for the SSV is up the back of thigh to the buttock and through the sciatic notch to the internal iliac vein. Veins at the back of thigh can contribute to complex patterns of disease and reflux. The TE is present in approximately 70% of limbs, is frequently as large as the SSV, usually extends to the middle or upper thigh, and terminates in almost equal proportions in deep or superficial veins.[4] The TE passes up the back of thigh in a groove between the semitendinosis and biceps muscles in a fascial compartment just as for the SSV and GSV.[1,8] Giacomini clearly showed that what is now termed the TE may terminate in veins in the buttocks, posterior thigh perforators, or superficial tributaries (see Figure 32.1).[1] A communication of the TE with the posterior circumflex thigh vein to connect to the GSV is now termed the vein of Giacomini. The terminal TE pierces the deep fascia if it passes to deep veins or passes superficial to the membranous fascia if it forms the vein of Giacomini.[8]

Saphenopopliteal Junction (SPJ)

The SPJ is the proximal end of SSV above the preterminal valve. The SPJ may be rudimentary and is absent in

approximately one-quarter of limbs, with flow continuing up the TE.[2,4]

The SPJ is within 4 cm above the knee skin crease in approximately two-thirds of limbs and it is usually higher than this level in the rest joining the proximal popliteal or femoral vein,[2] although a low junction or termination in the upper calf to the gastrocnemius veins or GSV has been described.[4] The SPJ is frequently medial or lateral to the midline.[10] Ultrasound has shown that the junction is on the posterior aspect of the deep vein in just 15%, to the medial or lateral side in approximately 85%, and even anterior in 1%.[11]

If an operation is to be performed to ligate the SSV flush with the popliteal vein then it is essential to know the junction is present and its exact location.

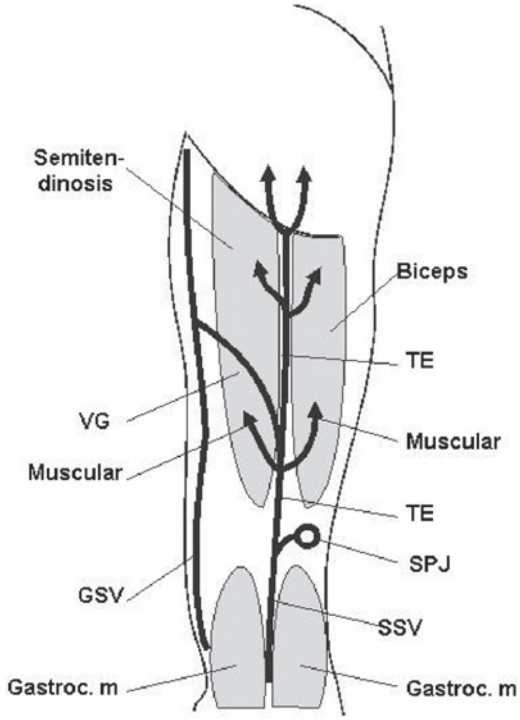

FIGURE 32.1 Course and terminations of the SSV and TE at the back of knee and thigh. VG, vein of Giacomini.

SURGICAL PATHOLOGY

Superficial and Deep Venous Reflux

Ultrasound shows that the larger proportion of limbs have superficial reflux with or without deep reflux and that deep reflux alone is uncommon, although the prevalence of deep reflux increases with increasing clinical severity (see Table 32.1).[3] The prevalence of SSV reflux increases according to the presence and extent of deep reflux.[5] Cavezzi and colleagues found that approximately three-quarters of limbs with SSV reflux had associated femoral or popliteal reflux and that this deep reflux usually was abolished by SSV surgery.[6] They also found that although most limbs show reflux after release of calf compression during ultrasound scanning, a few show flow through the SPJ during calf compression, particularly where the destination for reflux is into the vein of Giacomini.[6]

Reflux in the SSV Territory

Approximately one-third of all limbs with saphenous reflux have reflux in the SSV territory and the proportion of limbs with SSV reflux increases with increasing severity of clinical disease (see Table 32.2).[3,5] There are various sites for reflux in the SSV territory, and the SPJ is competent in approximately one-third of limbs with reflux from other connections (see Table 32.3).[2,6] Aneurysmal dilatations are common along the length of the SSV.[12]

SSV reflux is a significant risk factor for recurrence of venous ulceration.[5] Ulcers associated with GSV reflux may be on any aspect of the leg, but ulceration over the lateral aspect of the ankle usually is associated with SSV reflux, often without associated pigmentation or eczema.[10]

Superficial thrombophlebitis of the SSV may have a higher incidence of associated contiguous or noncontiguous deep venous thrombosis than for the GSV, occurring in approximately two-thirds of patients in one ultrasound study.[13]

Reflux in the TE and Vein of Giacomini

Ultrasound has shown that reflux in the TE and vein of Giacomini is far more likely to occur in association with

TABLE 32.1 An Ultrasound Study of Proportions of Limbs with Reflux in the Superficial and Deep Veins in Relation to the Clinical Severity of Venous Disease (Myers and colleagues—unpublished data)

Venous reflux	C2–3 number	%	C4–6 number	%	Total number	%
Superficial alone	1626	89%	65	42%	1691	85%
Superficial and deep	172	9%	73	47%	245	12%
Deep alone	29	2%	16	11%	45	3%
Total	1827		154		1981	

TABLE 32.2 An Ultrasound Study of Proportions of Limbs with Reflux in the GSV or SSV in Relation to the Clinical Severity of Venous Disease (Myers and colleagues—unpublished data)

Superficial reflux	C2–3 number	%	C4–6 number	%	Total number	%
GSV alone	1255	70%	65	47%	1320	68%
SSV alone	242	13%	31	23%	273	14%
GSV & SSV	301	17%	42	30%	343	18%
Total	1798		138		1936	

TABLE 32.3 An Ultrasound Study of the Sources and Destinations of Reflux into the SSV Territory (Myers et al.[3])

	Distal destinations				
Proximal connections	SSV only	SSV & VG	VG only	SSV tributaries	Total proximal connections
SPJ only	169	11	5	1	186 (56%)
SPJ & VG	10	—	—	—	10 (3%)
VG only	54	—	—	1	55 (17%)
GSV tributaries	55	—	—	2	57 (17%)
Perforators	11	—	—	—	11 (3%)
Unknown	15	—	—	—	15 (4%)
Total distal destinations	314 (94%)	11 (4%)	5 (1%)	4 (1%)	

TABLE 32.4 An Ultrasound Study of the Frequency of Association between Reflux in the TE or Vein of Giacomini and Reflux in the GSV or SSV (Georgiev et al.[2])

Saphenous reflux	Number	Number with TE reflux	% with TE reflux
GSV alone	922	6	1%
SSV alone	138	23	17%
GSV & SSV	166	47	28%
Total	1226	76	6%

SSV than GSV reflux (see Table 32.4).[1,4] Saphenofemoral or pelvic vein incompetence can result in proximal to distal flow to the SSV through the TE or vein of Giacomini, and saphenopopliteal incompetence can result in distal to proximal flow through these veins from the SSV to GSV or thigh tributaries (see Figure 32.2).[1]

Gastrocnemius Vein Reflux

Reflux into gastrocnemius veins is reasonably common.[14] It may be symptomatic, causing aching from calf congestion; this is frequently without evidence of superficial varicose veins. Treatment may require flush ligation at the junction with the popliteal vein or excision of the terminal SSV if the gastrocnemius veins drain to the SSV. However, recurrence after ligation is common due to failure to ligate all connections or revascularization.[14]

Outward Flow in Perforators

We detected outward flow in perforators in the calf in 30% and thigh in 4% in limbs with SSV reflux and primary varicose veins, and this was not significantly different from limbs with GSV reflux.[2] There is debate as to whether perforators with valvular incompetence are an avenue for outward flow into superficial varicose veins or whether perforators act as safety valves for blood to escape from diseased superficial veins to be removed through normal functioning deep veins.

TABLE 32.5 An Ultrasound Study of the Sources and Destinations for Reflux through the TE or vein of Giacomini from Proximal Sources to the SSV or from the Distal SSV to Proximal Destinations (Georgiev et al.[2])

Source of reflux	Destination of reflux	Number with TE reflux	% with TE reflux
GSV	SSV	15	20%
Thigh veins	SSV	18	24%
Pelvic veins	SSV	20	26%
Total distal reflux			70%
SSV	GSV	18	24%
SSV	Thigh veins	5	6%
Total proximal reflux			30%

Mechanisms for Reflux

Ultrasound shows that in most limbs, SSV reflux is associated with one or more intact valves in deep veins above the SPJ or indeed at the junction itself. There is no large central pool of blood for reflux into the SSV. The routine maneuvers of calf compression or cuff inflation during ultrasound scanning result in approximately 20 to 30 ml of blood refluxing from the deep veins to SSV if the SPJ is incompetent. This equates to the volume in a 5 to 10 cm length of

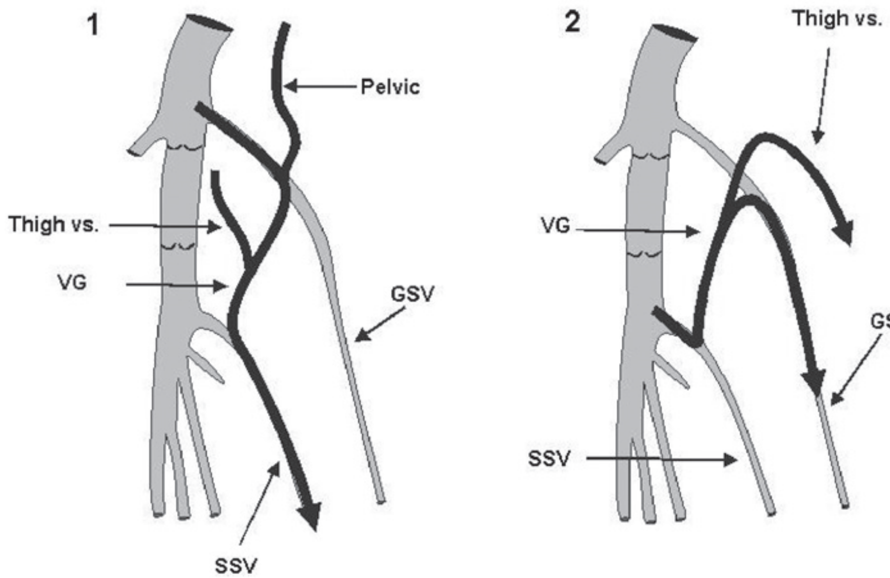

FIGURE 32.2 Reflux through the vein of Giacomini from the GSV territory to the SSV (1) and from the SSV to the GSV territory (2).

deep vein above and below the junction that acts as the reservoir for flow. This is approximately the length expected in the adjacent deep veins between competent valves.

Ultrasound examination is the standard method to detect SSV reflux and advise appropriate treatment. However, it is probable that the examination bears little relation to the everyday hemodynamics during standing and walking, which are poorly understood. Current concepts hold that the primary abnormality for varicose disease commences in the saphenous veins and tributaries, with secondary functional valvular incompetence in many limbs as dilatation reaches the proximal junctions. Accordingly, it would be naive to anticipate that simple interruption at the junction would restore normal venous function. There is undoubtedly a complex interaction of antegrade and retrograde flow through the SSV and deep veins, and flow in either direction through some calf perforators in the presence of disease. This suggests that destruction of the entire diseased segment of SSV and TE is required for best results from treatment. This is not common surgical practice.

DIAGNOSIS

Clinical

Inspection, palpation, and the percussion test may reveal a dilated SSV or tributaries behind knee in the SSV territory, but provide no information regarding the SPJ. Tourniquet tests are of little value for reflux into the SSV if there are competent valves in deep veins above the SPJ preventing deep reflux, as is very frequently the case. Even if there is full length deep reflux, it is difficult to be sure that a tourniquet selectively occludes superficial veins and not deep veins. Interpreting results in patients with combined GSV and SSV reflux is difficult.

Continuous-Wave (CW) Doppler

The handheld CW Doppler probe is considered by many to be a convenient way to record popliteal vein or SSV reflux, but it will provide false-positive results that could lead to unnecessary popliteal fossa exploration in at least 10%.[15] CW Doppler cannot define variations in anatomy and in particular the information required regarding the SPJ. CW Doppler is widely used to exclude SSV reflux because it has a low false-negative rate, but this seems pointless if the policy is to perform routine duplex ultrasound scanning.

Duplex Scanning

Many surgeons now routinely request a duplex ultrasound scan prior to treatment for varicose veins.[16] Anatomy needs to be defined prior to treating SSV reflux. However, results are reliable only if performed by specialist vascular sonographers or sonologists. A survey from the Vascular Surgical Society of Great Britain and Ireland[17] found that 90% of surgeons obtained duplex scans in all patients with suspected SSV reflux. In addition, approximately 60% routinely obtained a further scan to mark the SPJ and SSV immediately before operation. A British report found that the preoperative scan did not improve outcome after SSV surgery, but the recurrence rate was high with or without preoperative scanning.[18]

Our technique is to examine with the patient standing and knee slightly flexed with weight taken on the opposite side and we prefer to test for reflux with manual calf compression and release. The routine scan for the SSV territory is to examine for pathology including:

- Incompetence at the SPJ
- Reflux in the popliteal vein proximal and distal to the SPJ, SSV down its full length, and gastrocnemius veins
- Alternative connections including the TE or vein of Giacomini, popliteal fossa perforators, GSV tributaries, intersaphenous veins or pelvic veins traced to the buttocks or perineum
- Alternative destinations for reflux including the TE or vein of Giacomini, or tributaries
- Diameters at the SPJ and along the SSV and TE if there is reflux
- The level of the SPJ in relation to the skin crease at back of knee if there is reflux
- The position of the SSV in relation to the midline axis in the popliteal fossa—midline, lateral, or medial if there is reflux

Venography and Varicography

A minority of surgeons use this technique prior to operation, either to help diagnose the presence of SSV reflux or to define the anatomy as the first step in theatre.

SURGERY FOR SSV REFLUX

Surgery generally is directed toward dividing the saphenopopliteal junction, presupposing that reflux through the junction is the cause of varicose veins in the SSV territory. Anatomical variations for patterns of reflux determine technique and results of surgery.

Indications

Surgery appears to be the most frequently recommended treatment for SSV reflux in most countries,[16] but many phlebologists now prefer endovenous techniques. Repeat surgery for recurrent SSV reflux to remove the saphenous stump or other connections is technically demanding and prone to complications from damage to the popliteal vein or adjacent nerves, and it is our practice to always recommend endovenous treatment.

Technique

The operation usually is performed under general anesthesia although spinal anesthesia or popliteal nerve and posterior nerve of thigh blocks can be used. Most surgeons operate with the patient prone and this requires intubation for general anesthesia. A transverse popliteal fossa incision is favored by most although an incision for a high SPJ can be disfiguring.

A survey of members of the Vascular Surgical Society of Great Britain and Ireland[17] found that most surgeons performed flush ligation although few extensively exposed the popliteal vein unless surgery was for recurrent SSV reflux. There was a degree of caution about the extent of surgery for only 15% routinely stripped the SSV, and approximately one-quarter simply ligated the vein and over one-half avulsed or excised as much as possible within the operation field. Practice patterns in other countries do not appear to have been documented.

Each surgeon has a favored technique:

- Flush ligation and division require precise identification of the point where the SSV joins the deep vein. It is important not to leave a stump particularly if it includes a tributary.
- Excision of the terminal SSV within the operation field is preferred by many to eliminate tributaries near the junction that could contribute to recurrence. Care must be taken to identify and ligate important veins such as the gastrocnemius veins if they join the SSV. Gastrocnemial vein ligation may be the indication for surgery.
- Retrograde stripping to mid calf or further may be performed, now favoring invagination stripping. There is no evidence as to whether stripping reduces recurrence rates or increases risk of nerve damage, or whether invagination reduces the incidence of sural nerve injury.
- Antegrade stripping from the ankle may be performed and the presence of the stripper in the SSV at the junction makes it easier to identify the veins. Care must be taken to avoid damage to the sural nerve during the distal dissection.

There is little support for routinely ligating perforators at the same time as SSV surgery. Outward flow in perforators is more frequently associated with superficial reflux alone rather than with deep reflux making it unlikely that they are a “source” for superficial tributaries.

Results

The small number of prospective studies published that used ultrasound for surveillance after SSV surgery show disturbingly high recurrence rates. Van Rij and colleagues reported that recurrence rates at three weeks and three years were 23% and 52%, respectively, after SSV surgery compared to 1% and 25%, respectively, after GSV surgery.[19] Smith and colleagues studied 37 limbs treated by SSV ligation with excision within the popliteal fossa and showed that the recurrence rate at 12 months was 38%, due to inadequate

surgery in 27% and neovascularization in 11%.[18] Another British report found an "ideal" outcome in only 39% of 67 limbs at six weeks, with persistent SSV reflux from tributaries in 20% and an intact patent SPJ in 36%.[20] A Dutch study found that only five of 32 limbs treated by SSV ligation were completely controlled at three months, with persisting reflux into adjacent tributaries in 14 and a patent junction in 13 limbs.[21] There is a need for larger prospective objective studies using ultrasound surveillance for outcome after ligation alone or ligation and stripping.

Sites for recurrence have been defined by retrospective ultrasound studies for recurrent varicose veins after SSV surgery. Tong and Royle showed an intact SSV to be the most common finding, with varices from the popliteal vein to residual SSV in the remainder.[22] Labropoulos and colleagues showed that the most common pattern after previous SSV ligation was reflux into the SSV (75%), whereas the most common pattern after previous SSV stripping was reflux into SSV tributaries (64%).[7]

Complications

Many surgeons use deep vein thrombosis prophylaxis selectively prior to varicose vein surgery, but few use it routinely.[16] However, the risk of deep vein thrombosis after SSV surgery has not been defined.

Nerve injury after venous surgery is the most common reason for medicolegal claims in vascular surgical practice.[23] A survey from the Vascular Surgical Society of Great Britain and Ireland found that nerve injury is perceived to be more likely after SSV surgery since two-thirds of surgeons were more likely to warn of this complication for SSV surgery compared to GSV surgery.[17] However, the incidence of sural or popliteal nerve injuries after SSV surgery has not been determined and may be low.[24] Damage to the sural nerve during SSV surgery probably results from straying away from the vein during dissection.

ENDOVENOUS TREATMENT FOR SSV REFLUX

Techniques are described in Chapters 29 and 31, and this chapter will summarize particular features relating to SSV reflux in our practice.

Ultrasound-Guided Sclerotherapy

Ultrasound-guided sclerotherapy (UGS) has been used by our group to treat 175 SSV systems in 144 patients. We favor foam sclerotherapy using sodium tetradecyl sulphate diluted with normal saline to a 1.5% concentration and then foamed in the ratio of two parts sclerosant to three parts air. Injection is made as far distal in the vein as possible controlling communications to deep veins at the SPJ or through large perforators with a finger or the ultrasound probe. It is usual to inject approximately 5 ml of foam to fill the SSV and its tributaries, although larger volumes can be safely given for very extensive varicosities.

Endovenous Laser Therapy and Radiofrequency Closure

Endovenous laser therapy has been used by our group for 45 limbs of 40 patients with SSV reflux using an 810 nm system. The procedure is performed under local anesthesia with a 10% xylocaine paste to a strip along the vein for 30 minutes followed by perivenous anesthesia with 0.2% xylocaine with adrenaline injected into the saphenous compartment at intervals along the vein. Perivenous fluid injection provides a heat sink and compresses the vein onto the probe as well as producing anesthesia. The system is set to deliver 14 watts power continuously and the withdrawal rate is 3 to 4 mm per second. Residual tributaries can be treated by UGS or by ambulatory phlebectomy. We can find no published reports describing a technique for radiofrequency closure for SSV reflux.

Postoperative Management and Surveillance

All limbs are bandaged or compressed with class II stockings for three days and then compressed with stockings during the day for two weeks. All patients are reviewed with ultrasound at three to seven days to confirm occlusion of the treated veins and to exclude deep vein thrombosis. They are then followed by ultrasound surveillance at six weeks, semiannually for two years, then annually.

Results

In our series, the primary success rate determined by ultrasound surveillance after UGS for SSV reflux was 55% at two years, but this improved to a secondary success rate of 77% with repeat UGS as required for clinical recurrence (see Figure 32.3). Results were significantly worse for younger patients (see Figure 32.4) and for veins greater than 5 to 6 mm diameter (see Figure 32.5). Dissatisfaction with the results of surgery has made UGS the preferred treatment for patients with small diameter refluxing SSVs or their tributaries as defined by routine ultrasound scanning. However, worse results with UGS for larger diameter veins lead us to prefer EVLT, particularly for younger patients.

After EVLT, we had technical failure in one limb and late recurrence at nine months in another, but all other limbs remain controlled at one to 30 months (median seven months). The only complications encountered were transient sural nerve palsy with full recovery in one limb and asymptomatic minor extension of a tongue of thrombus into the

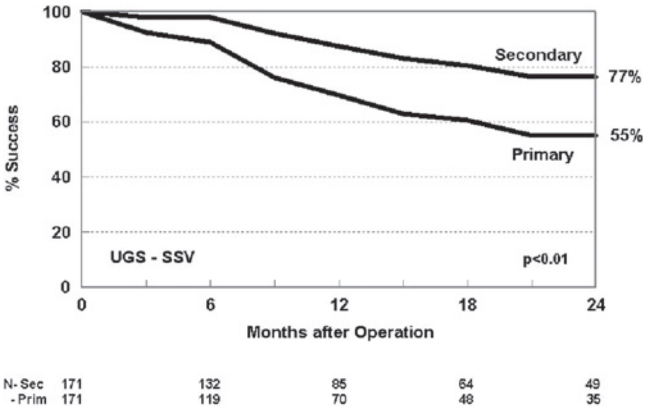

FIGURE 32.3 Life table analysis of primary and secondary success rates from ultrasound surveillance for ultrasound-guided sclerotherapy for the SSV.

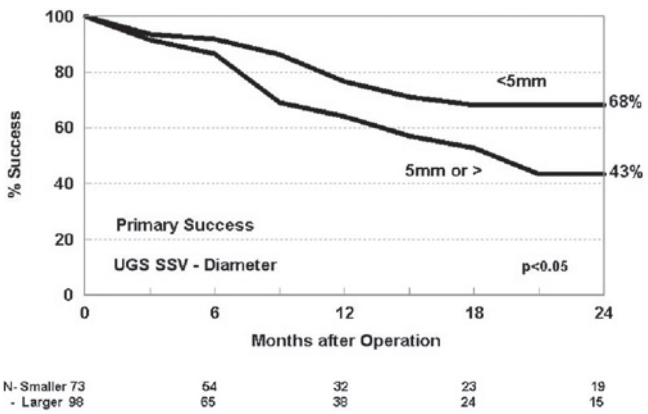

FIGURE 32.4 Life table analysis of primary success rates from ultrasound surveillance for ultrasound-guided sclerotherapy for the SSV according to the patients' ages.

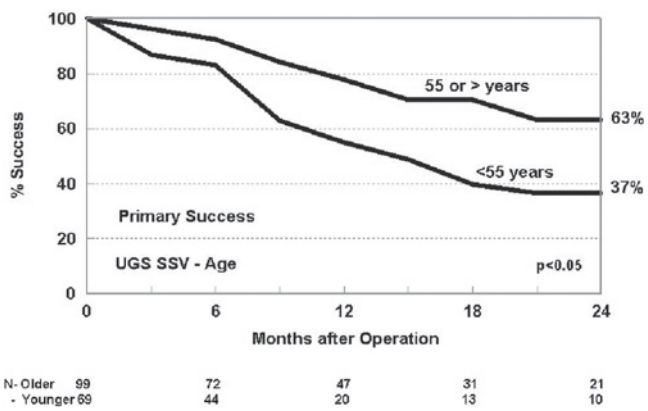

FIGURE 32.5 Life table analysis of primary success rates from ultrasound surveillance for ultrasound-guided sclerotherapy for the SSV according to the vein diameters.

popliteal vein in another. Proebstle and colleagues published results for EVLT in 41 limbs with SSV reflux, and found initial success in 95% and no subsequent recanalization in any limb determined by ultrasound surveillance at a median six-month follow-up.[25] The single complication reported was a popliteal vein thrombosis that resolved. These results persuade us to favor EVLT for SSV reflux where the vein has been shown to be straight and of diameter greater than an arbitrary 5 mm.

There have been no published reports documenting results after treatment by radiofrequency closure for SSV reflux. It is understood that there was an unacceptable risk of transient sural neuralgia in the early stages and that this has been reduced but not eliminated by perivenous anesthesia.

CONCLUSION

The hemodynamics of SSV reflux are poorly understood. The concept of a "source" of reflux from a deep venous pool does not seem to be valid. Retrograde flow into the SSV is probably simply an expression of the capacity in the dilated veins. The variable anatomy and reflux patterns are probably responsible for the wide variation in treatment techniques and poor results from surgery. Better techniques need to be defined to improve surgical outcome if it is to remain the preferred technique for treatment. Otherwise new endovenous techniques will replace surgery as experience grows.

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CHAPTER

33

Classification and Treatment of Recurrent Varicose Veins

MICHEL PERRIN

INTRODUCTION

Recurrence varices after surgery (REVAS) are a common, complex, and costly problem both for the patients and the physicians who treat venous diseases. To deal with this problem an international consensus meeting was held in Paris in 1998, which proposed guidelines for the definition and description of REVAS.[1]

In this article 94 references were listed. Since 1998 many valuable new studies have been published.[2–23]

DEFINITIONS

According to Browse et al.,[24] it is important to distinguish between residual veins and recurrent veins.

> Residual veins are varicose veins that were not treated at the original operation, because they were not detected preoperatively, not found during the operation or were deliberately left untreated. Recurrent varicose veins are veins which have become varicose after the initial treatment having been normal at the time of that treatment.

This definition is true from a theoretical point of view but for the patient any kind of varices after surgery are considered a failure and usually termed recurrence. Consequently we decided at the REVAS consensus conference to define REVAS "The presence of varicose vein in a lower limb previously operated for varices with or without adjuvant therapies." This is a clinical definition, which includes true recurrences, residual veins, and varicose veins as a consequence of progress of the disease.

EPIDEMIOLOGY AND SOCIOECONOMIC CONSEQUENCES

Prevalence and Incidence of REVAS

They are not easy to determine as most studies are retrospective, analyzing patients that were not evaluated preoperatively by duplex scanning (DS), and usually the detailed operative report is not available. In a 34-year follow-up,[12] varicose veins were present in 77% of the lower limb examined and were mostly symptomatic. Fifty-eight percent were painful, 83% had a tired feeling and edema had reappeared in 93%.

Two recently published prospective studies are available with a follow-up of five years.[16,20]

In both, the patients had preoperative DS and were treated by high ligation, saphenous trunk stripping, and stab avulsion.

In the Kostas series from Crete,[16] true recurrent varices were present in eight limbs (8/28, 29%), primarily caused by neovascularization, new varicose veins as a consequence of disease progression were seen in seven limbs (7/28, 25%), residual veins were found in three limbs (3/28, 11%) mainly due to tactical errors (e.g., failure to strip the GSV), and complex patterns were identified in 10 limbs (10/28, 36%).

In the limbs with recurrence, 42 sources of venous reflux were identified: 19 new sites of venous reflux were due to disease progression, 15% of the operated limbs; 13 were caused by neovascularization, 11.5% of the operated limbs; six resulted from tactical failures, 5.3% of the operated limbs; and four were due to technical failures, 3.5% of the operated limbs. This study showed that recurrence of varicose veins after surgery is common. However, the clinical

condition of most affected limbs remains improved. Progression of the disease and neovascularization are responsible for more than half of the recurrences. Rigorous evaluation of patients and assiduous surgical technique might reduce recurrence due to technical and tactical failures.

In the van Rij series[20] from New Zealand, 127 limbs (C2–C6) were evaluated postoperatively by clinical exam, DS, and air plethysmography (APG). Clinical varices recurrence was progressive from three months onward (13.7%) to five years (51.7%). Corresponding to clinical changes there was a progressive deterioration in venous function measured by APG and recurrence of reflux evaluated by DS.

The longest prospective study[22] gives a REVAS rate of 62% at 11 years and there was no statistical difference between the HL-only and the HL+GSV trunk stripping+ phlebectomies, but the patients were assessed preoperatively by handheld Doppler.

A prospective study concerning recurrence after radiofrequency procedure has been reported.

At four-year follow-up recurrence is estimated at 21%.[25]

Socioeconomic Consequences

There are no available published socioeconomic data on REVAS. The incidence is variable according to the different National Health Service reimbursement rates. When redo surgery is performed its cost is higher than first time surgery because of the number of peri- and postoperative complications.

DIAGNOSIS

Modes of Presentation

Patients who have previous surgical treatment may consult their physicians for various reasons: unsightly recurrent varicose veins or related emotional problems, which are especially common in female patients; discomfort (in other words venous-related symptoms); appearance of cutaneous or subcutaneous changes; concerns about the health risk related to their veins; or limitation of activity. Also, REVAS may be found at routine follow-up.

Medical History

Family and Personal History

Family history of varicose veins and personal history including pregnancies, hormone therapy, superficial thrombophlebitis, deep vein thrombosis, and so on should be recorded.

Previous Treatment

The date of previous surgical treatment(s) for varicose veins, the age of the patient at the time of surgery, the name of the surgeon and the place of the operation in order to retrieve the operative record, postoperative surgical complication, date of the onset of recurrence, and reappearance of symptoms have to be documented, as does other treatment received after initial surgery (e.g., phlebotonic drugs, sclerotherapy, use of compression stockings, and leg elevation).

Physical Examination

Presence and intensity of the various vein-related symptoms have to be noted: pain, throbbing, heaviness, itching, feeling of swelling, night cramps, heat or burning sensations, or restless legs.

Inspection and palpation allow filling in the C of the CEAP classification, but it must be kept in mind that some signs such as corona phlebectatic are not described in the CEAP. Edema should be quantified.

The presence of scars on the lower limb must be noted, especially at the groin or popliteal fossa. Neurological abnormalities and particularly numbness have to be documented. Efficiency of the calf pump has to be assessed, particularly degree of ankle motion. Arterial pulses should be checked and ankle brachial index calculated.

A general examination including abdominal palpation should be performed, and possible obesity can be identified by BMI calculation.

Investigation

Many investigations have been used in the past to assess REVAS. At the moment there is a large consensus for recommending DS in all cases. This investigation provides anatomical and hemodynamic data including

- The topographical sites of REVAS that can be mapped
- The possible sources of reflux from the deep venous system to the superficial
- The intensity or degree of reflux
- The nature of sources keeping in mind that causes have to be classified differently if recurrence occurs in a site previously operated or not.

In addition DS gives information on perforator and deep venous systems that must be assessed in patients with REVAS.

One problem remains: a standardized DS investigation protocol is not universally used by the different investigators. A written investigation protocol consensus has to be tailored when dealing with REVAS. In very few cases venography, including descending venogram and three-dimension imaging, may give complementary valuable information.[26]

Other investigations such as APG and AVP may be useful for research studies but not for daily practice.

Quality of Life Questionnaires

To determine whether REVAS affect patients' quality of life, the health-related quality of life (HRQL) score of patients can been used in different ways for clinical studies. Beresford[2] compared patients presenting with REVAS versus patients with untreated varicose veins. No survey has compared operated patients with or without REVAS.

CLASSIFICATION

Many classifications have been developed concerning REVAS,[24,27] but they have not been widely used. One of their main goals was to identify if redo surgery, particularly at the previous saphenofemoral and saphenopopliteal junctions, must be part of the REVAS treatment. As will be shown later, indications have changed and this point is less important than it was previously. At the consensus meeting[1] we decided to use both the previously reported CEAP classification[28] and a specific classification named the REVAS classification. This new classification was intended to serve everyday clinical practice as well as in research studies into epidemiology, clinical status, and treatment of recurrent varicose veins. A survey was undertaken in order to test its intraobserver and interobserver reproducibility.[29] The conclusion of this study was that intraobserver reproducibility is quite satisfactory, and making slight changes in the answers to one question might increase interobserver reproducibility. However, the fact that interobserver reproducibility was less than intraobserver reproducibility reflects conditions of real life, and especially interobserver differences. Such interobserver differences may arise from interobserver technical differences, but this finding emphasizes the need for validating a duplex scanning protocol and standardizing duplex scan reports.

The REVAS classification (see Table 33.1) includes six items: T is for topographic sites of REVAS; S for sources of reflux; R for degree of reflux; N for nature of sources (Nss for same site of previous surgery, and Nds for different sites); P for contribution from a persistent incompetent saphenous trunk; and F for possible contributory factors (Fg for general and Fs for specific factors).

T is for topographic sites of REVAS. Recurrent varices should be localized at five sites: g is for groin, t for thigh, p for popliteal fossa, l for lower leg including ankle and foot, and o for other. Since that more than one territory may be involved in the same limb, topography gives a degree of quantification as to the extent of the recurrences.

S is for sources of reflux. It is considered important to identify the sources of reflux from the deep system when it is present. 0 is for no identified source of reflux, 1 for pelvic or abdominal, 2 for saphenofemoral junction, 3 for thigh perforators, 4 for saphenopopliteal junction, 5 for a popliteal perforator, 6 for gastrocnemius veins, and 7 for lower leg perforators. Several sources of reflux should be identified.

R is for degree of reflux. Although it is recognized that there are limitations for quantifying the degree of reflux according to parameters (duration, volume, mean peak velocity), it has not been proven that additional present reflux is valuable. However, the clinician should estimate the clinical significance of reflux. This estimate should be based on DS information and how the degree of reflux relates to the overall clinical situation.

R+ is for clinical significance probable, R− is for clinical significance unlikely, R? for clinical significance uncertain.

It is worthy of note that in the international survey interobserver R reproducibility was moderate but the intraobserver R was reliable.[29]

N is for nature of sources. This letter classifies the source as to whether or not it is the site of previous surgery and describes the cause of the recurrence.

Ss is for the same site that means the recurrence occurred in a territory where the previously superficial veins were operated on, and one of the five items may be chosen for NSs: 1 technical failures (see Figure 33.1), 2 tactical failures, 3 neovascularization (see Figure 33.2), 4 uncertain or unknown, 5 mixed.

Ds is for different (new) site. In other words when varices are present in a territory not previously operated, one of the three items may be selected for NDs: 1 persistent (known to have been present at the time of the previous surgery and not treated), 2 new (known to have been absent at the time of previous surgery), 3 uncertain or not known (insufficient information on the preoperative status before the previous surgery). As it might be foreseen in a retrospective study using REVAS classification, two-thirds of the patients were classified uncertain or not known and both the intraobserver and interobserver reproducibility was moderate.[29]

A precise answer to N in the REVAS classification should be anticipated in a prospective study, and, if used by dedicated physicians looking at their own patients before and after treatment, it might work very well.

C is for contribution from persistent incompetent saphenous trunks: GSV AK (above knee), GSV BK (below knee), SSV; O other, N neither.

F is for possible contributory factors that should be gathered and reported in the REVAS file: gF (general factors):

TABLE 33.1 REVAS Classification Form

Date of examination ⎵⎵ Day ⎵⎵ Month ⎵⎵⎵⎵ Year

Patient Name:
—First name or given name ⎵⎵⎵⎵________________
—Last name or family name ⎵⎵⎵⎵________________

T Topographical sites of REVAS
Since more than one territory may be involved several boxes may be ticked
- g Groin ☐
- t Thigh ☐
- p Popliteal fossa ☐
- l Lower leg including ankle and foot ☐
- o Other ☐

S Source(s) of Reflux
Since more than one source may be involved several boxes may be ticked
- 0 No source of reflux ☐
- 1 For pelvic or abdominal ☐
- 2 Saphenofemoral junction ☐
- 3 Thigh perforator(s) ☐
- 4 Saphenopopliteal junction ☐
- 5 Popliteal perforator ☐
- 6 Gastrocnemius vein(s) ☐
- 7 Lower leg perforator(s) ☐

R Reflux (Degree of Reflux)
Only one box can ticked
- PROBABLE Clinical significance R+ ☐
- UNLIKELY Clinical significance R− ☐
- UNCERTAIN Clinical significance R? ☐

N Nature of sources
Only one box can be ticked
N classifies the source as to whether or not it is the site of previous surgery and describes the cause of recurrence.
N Ss is for same site ☐
Only one box can be ticked
- Technical failure ☐
- Tactical failure ☐
- Neovascularization ☐
- Uncertain ☐
- Mixed ☐

N Ds is for different (new) site ☐
Only one box can be ticked
- Persistent ☐
  (Known to have been present at the time of previous surgery)
- New ☐
  (Known to have been absent at the time of previous surgery)
- Uncertain/not known ☐
  (insufficient information at the time of previous surgery)

C Contribution from persistent incompetent saphenous trunks
Since more than one territory may be involved several boxes may be ticked
- AK great saphenous (above knee) ☐
- BK great saphenous (below knee) ☐
- SSV small saphenous ☐
- O Other ☐
- N Neither ☐
- Comment . . . .

F Possible contributory factors
Several boxes may be ticked
gF General factors
- Family history ☐
- Obesity ☐
- Pregnancy ☐
- Oral contraceptive ☐
- Lifestyle factors ☐
- Pregnancy since the inital operation ☐
- Professional activity ☐
- Other . . . .☐

sF Specific factors
Several boxes may be ticked
- Primary deep vein reflux ☐
- Post thrombotic syndrome ☐
- Iliac vein compression ☐
- Congenital vascular malformation ☐
- Lymphatic abnormality ☐
- Calf pump dysfunction ☐
- Other . . . .☐

family history, obesity, pregnancy, oral contraceptive, lifestyle factors (pregnancy since the initial operation, professional activity, other). sF (specific factors): primary deep venous incompetence, post-thrombotic syndrome, iliac vein compression, congenital vascular malformation, lymphatic abnormality, calf pump dysfunction, other.

TREATMENT

Methods

Compression

Compression in varicose veins is frequently recommended and improves both symptoms and signs, but it does not cure the disease.

Drugs

In varicose veins phlebotonic drugs are prescribed mainly to improve edema and symptoms. The most commonly used are flavanoids, but others exist.

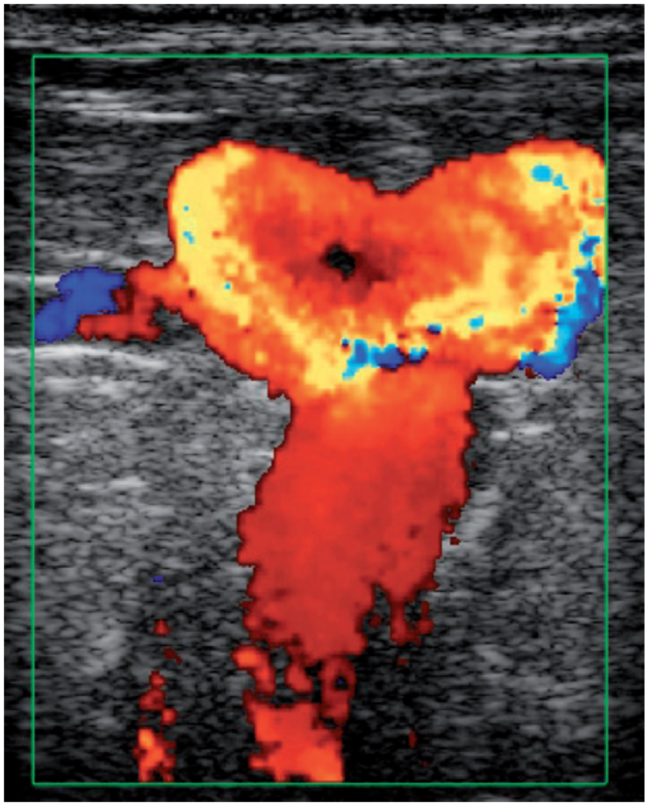
Interventional Procedures

They share the same goals:

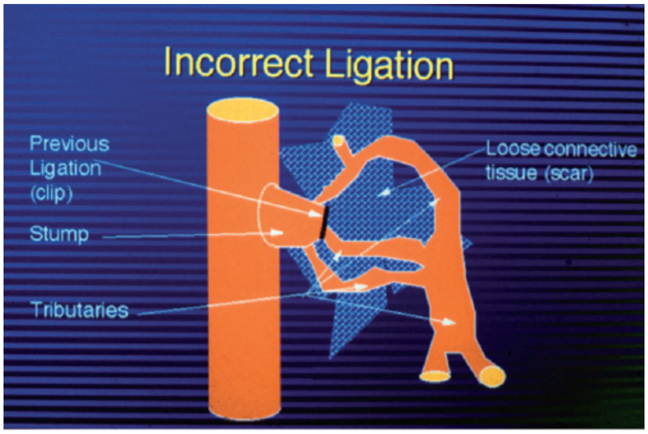
- To eliminate reflux from deep to superficial systems when they do exist
- To eliminate varices
- In some specific cases, to suppress deep vein abnormality to prevent new recurrences

The final objective is multiple: decrease the ambulatory venous pressure, prevent worsening of chronic venous

A B



C



D

FIGURE 33.1 REVAS related to a nonflush resection of the saphenofemoral junction in a patient with an incompetent terminal valve. **A**. Patient view. **B**. Same patient. Reflux at the saphenofemoral junction through the saphenous stump illustrated by inducing a Valsalva maneuver during a dynamic popliteal phlebography. **C**. Same patient. Color duplex ultrasound. Massive reflux induced by a Valsalva maneuver. **D**. Same patient, scheme.

disorders, avoid further recurrences, and of course, improve the patients in terms of cosmetic appearance, symptoms, and signs.

Sclerotherapy

Sclerotherapy has been used for a very long time for treating REVAS, but ultrasound-guided sclerotherapy (USGS) has improved the technique. Different protocols have been used but no comparative study is available. Recently foam USGS has entered the ring, but no consensus exists on the techniques, doses, concentrations, or sclerosing agents. Nevertheless one of the main advantages of sclerotherapy with or without foam is that the process is simple and repeatable.

Surgery

Procedures can be classified into three groups according to their objective, and should be used in combination.

The first group gathers techniques that aim to eliminate reflux from deep to superficial systems. At the saphenofemoral or saphenopopliteal junctions, the site usually has been previously operated, and according to the extent of postoperative fibrosis, redo surgery may be difficult. It is recommended to approach the deep vein first in order to avoid dissection of scar tissues, lymphatic nodes, and cavernoma. Flush ligation of the stump and patch interposition is recommended.[9]

The second procedure of this group consists of perforator ligation. When severe cutaneous and subcutaneous changes

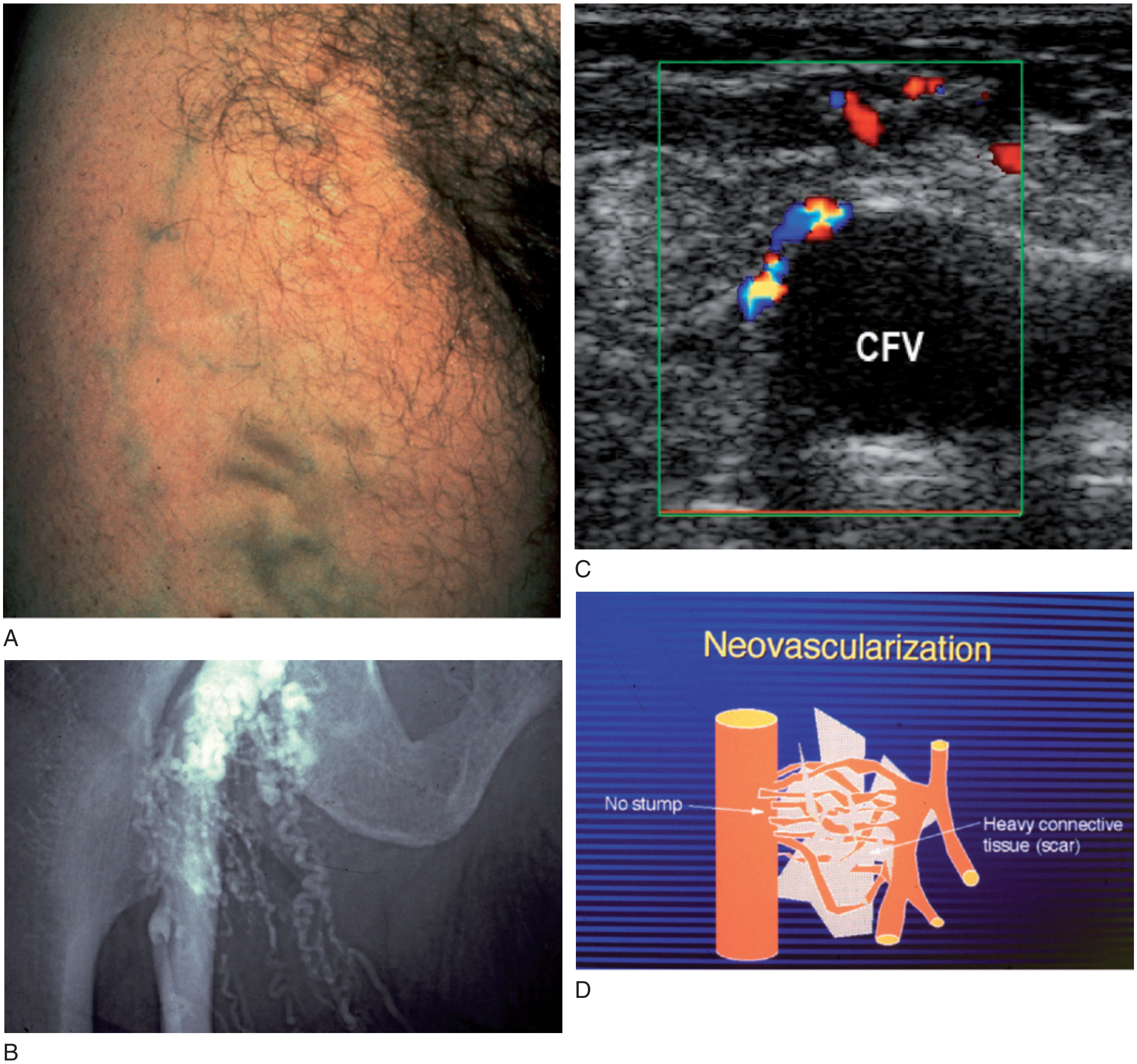


FIGURE 33.2 REVAS related to neovascularization in a patient who had a flush resection of the saphenofemoral junction. **A**. Patient view. **B**. Same patient. Reflux at the saphenofemoral junction through multiple small caliber channels by inducing a Valsalva maneuver during a dynamic popliteal phlebography. **C**. Same patient, duplex scanning. Reflux induced by a Valsalva maneuver is identified in several small caliber channels. **D**. Same patient, scheme.

are present, subfascial endoscopic perforator surgery (SEPS) is the favored technique.

The second group includes procedures that aim to eliminate or obliterate the refluxing varices. According to the location and type of varicose veins, various techniques can be used: stab avulsion and phlebectomy are the most used techniques, and stripping or endovascular obliteration (laser, radiofrequency) usually are reserved for treating the residual saphenous trunk.

The third group is represented by procedures whose goal is to suppress deep vein reflux, as several studies demonstrated that primary extended deep incompetence (reflux grade 4 according to Kistner) frequently is associated with REVAS.[30,31]

Embolization and Coils

In patients whose varices are fed by pelvic or gonadal reflux this procedure has now replaced direct ligation.[17]

Results

Compression and Drugs

We have no specific data on the efficacy of compression treatment and drugs in patients with REVAS.

Sclerotherapy

The efficacy of sclerotherapy using one protocol has been reported on a large series (253 legs) with a follow-up of 3.1 ± 1.7 years (range 1.5–5.7 years).[18]

The cumulative obliteration rate was sustained at >90% and there was a significant decrease in the venous dysfunction score. Unfortunately the endpoint of sclerotherapy sessions is not given.

No data have yet been published with foam techniques.

Surgery

Surprisingly very few data are available on the results provided by redo surgery in patients investigated preoperatively with DS.

I reported a series of 145 limbs with a five- to six-year follow-up.[32] All had major reflux from the deep system feeding recurrent varices that were treated by surgery. Postoperative sclerotherapy was performed in all patients during the first two years. An external audit revealed a global objective improvement of 85%, but there was better improvement of signs and symptoms than cosmetic appearance.

The results of two studies using an interposition patch for treating recurrence at the saphenofemoral junction (SFJ) have been published. Creton,[5] using this procedure without resection of the groin cavernoma but with combined resection of varices (saphenous trunks and/or tributaries), had only 4.2% recurrences at the SFJ at 4.9 years mean follow-up (range 3 to 7 years) in 119 extremities. Nevertheless, 22.6% of patients had diffuse varices, with a new site of incompetence between the deep and femoral systems.

De Maeseneer[9] has compared the results at five years of two nonrandomized groups with and without patch in a prospective study. All patients had recurrent SFJ incompetence.

The results were significantly better in terms of absence of recurrent thigh varicosities and neovascularization in the patch group.

Embolization

At six months follow-up, 90% of 215 patients treated by embolization of gonadal and pelvic veins were significantly improved in both signs and symptoms.[17]

Indications for Treating REVAS

Patients with REVAS can be roughly divided into two groups:

- Patients complaining of symptoms or esthetic concerns, or presenting with signs of chronic venous disease (C2–C6). In all cases these patients need to be investigated by DS.
- Subjects attending a routine follow-up. The decision whether to undertake DS or not depends on the presenting complaint and physical findings. In practice DS is almost always done.

Asymptomatic Patients

When hemodynamic abnormalities are found in asymptomatic patients without severe signs who are not concerned by their minor varices as cosmetic problems the decision to treat depends of the severity of the noninvasive findings. In all cases follow-up is required knowing that abnormal DS findings precede symptoms and signs.

Symptomatic Patients

In symptomatic patients presenting with recurrent varices and hemodynamic anomalies, treatment must be considered. At the REVAS conference in 1998 we agreed that there was no consensus for recommending sclerotherapy, surgery, or a combination of both when active treatment was needed. Seven years later one cannot provide either grade A or B recommendations.

Sources of Reflux

Concerning the treatment of sources of reflux, surgery was considered the best option in patients where a major reflux was identified at the SFJ, but there is no evidence that USGS does not give the same results. If redo surgery is undertaken a silicone or PTFE patch on the common femoral vein is recommended.

In the presence of recurrent reflux at the saphenopopliteal junction, sclerotherapy generally is used since redo surgery is sometimes difficult, but again there is no evidence that one method is better than the other.

Thibault reported early favorable results when treating incompetent perforators with USGS.[33] This method is popular when dealing with recurrent varices fed by leg or thigh perforators, but in patients with ulcer SEPS it is the recommended method.

Major pelvic reflux is a good indication for embolization, but minor reflux can be treated as a first step by USGS.

The Varicose Network

When a persistent incompetent saphenous trunk is present, pin stripping or endovenous procedures (laser, RF) or USGS are possible options according to the experience and habits

of the practitioner. For other varices USGS and stab avulsion are appropriate.

Ferrara[11] relies on preprocedural bandage efficacy to compress the recurrent veins for treating patients with sclerotherapy.

Associated Deep Reflux

In patients with primary deep vein reflux grade 4 and C 4b–6, valvuloplasty must be considered in active patients reluctant to wear lifelong compression or with recurrent ulcer.[1]

GUIDELINES FOR PROSPECTIVE STUDIES

In order to know the prevalence and annual incidence of REVAS we need prospective studies well documented in detail from the outset of surgical treatment as in Kostas' series.[16]

These studies may give information on:

- The value of routine postoperative scanning in the early detection of persisting reflux;
- The relationship between hemodynamics and clinical recurrence;
- The possible role of compression therapy and/or complementary postoperative sclerotherapy in preventing recurrence;

To identify what is the best method, when REVAS has occurred, prospective randomized studies using different treatments are needed. These studies may use both the updated CEAP and REVAS classification and a quality of life questionnaire.

CONCLUSION

REVAS is a frequent condition frustrating both patients and physicians that has been poorly evaluated. In order to build a scientifically convincing evidence base and to achieve a greater degree of comparability between studies, an international consensus on conformity is required.

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CHAPTER

34

Use of System-Specific Questionnaires and Determination of Quality of Life after Treatment of Varicose Veins

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INTRODUCTION

Varicose veins are one of the most common conditions in the Western world. In the United Kingdom approximately 100,000 varicose vein operations are performed per annum. Long saphenous vein surgery accounts for 90%, with recurrent surgery accounting for 20% of procedures.[1]

Results from the Edinburgh Vein Study estimated the prevalence of trunk varices to be one third in men and women aged 18 to 64 years.[2] Spider and reticular veins were noted in 80% of the population. This study was unusual in that it identified a significantly higher prevalence of truncal veins in men compared with women; a possible explanation for this was that previous studies relied on self-assessment of varicose veins and this resulted in bias because women are more likely to consult for this condition than men. In the United States a longitudinal study of a community reported the prevalence of any varicose veins as 25.9% and 12.9% in women and men, respectively.[3]

Lower limb venous disease not only causes morbidity but is expensive; it is estimated that 2% of national health care resources are spent on treatment.[4] Evidence on the effectiveness of various interventions for venous problems is not clear and the assessment of patient outcome is lacking.[5] The standard method of assessment incorporates quality of life questionnaires.

Quality of Life

Quality of life as defined by the World Health Organization is a state of complete physical, mental, and social well-being, and not merely the absence of disease. However Price described quality of life as the impact of an illness and its treatment on disability and daily living.[6] Quality of life assessment is of value in demonstrating the benefit of interventions in patients and can be used to measure the benefit gained and plan future treatment.

The criteria for an ideal quality of life measure are:

- Equally applicable to any disease process or outcome
- Equally applicable across all levels and degrees of invalidity
- Proven validity with a high level of convergence within patient groups when applied across geographic, linguistic, and cultural boundaries[7]

Improving quality of life has become a major focus of interest in medicine; however, most outcome measures assess much narrower concepts such as impairment and disability. In 1984 a definition of quality of life offered was "the extent to which our hopes and ambitions are matched by our experience."[8] This definition tries to reduce the gap between patients' expectations and actual results.

Currently there is no single quality of life tool that fulfills this criteria; this means that a generic tool has to be adopted. Options include the Nottingham Health Profile (NHP), EuroQol (EQ), Frenchay Activities Index (FAI), or McGill Short Form Health Survey (SF-36). The International Quality of Life Assessment (IQOLA) project was an undertaking to translate and adapt the SF-36 questionnaire and validate it in all major languages, thereby making it an international scale of health-related quality of life.[9]

Instruments used to measure quality of life are classified into generic and disease-specific instruments. Generic instruments allow comparison across populations of patients with different diseases, whereas disease-specific instruments are sensitive to key dimensions of quality of life that are affected by specific diseases. Therefore combining the two is the preferred strategy when examining quality of life.

TABLE 34.1 The Venous Clinicial Severity Score

Characteristic	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Varicose veins	None	Few	Multiple	Extensive
Edema	None	Evening ankle edema	Afternoon above ankle edema	Morning edema above ankle
Pigmentation	None	Limited and old	Diffuse gaiter area	Wider distribution
Pain	None	Occasional	Daily	Limiting activities
Inflammation	None	Mild	Moderate	Severe
Induration	None	<5 cm	<lower third of leg	All of lower leg
Acute ulcers (number)	None	1	2	>2
Duration of ulceration	No	<3 months	>3 months	>1 year
Diameter of ulcer	No	<2 cm	2–6 cm	>6 cm
Compression used	Nil	Occasionally	Most days	Every day
Maximum Score				30

Measurement of Outcome

In developing an outcome measure the concepts of validity, reliability, and responsiveness are vital.

Validity is the extent to which a questionnaire measures what is intended. This usually is assessed by comparing a new measure with an established one (this is known as criterion validity). In the absence of a gold standard, construct validity can be measured; this allows comparison of a new tool with objective or clinical findings.

Reliability is the degree to which measurements on the same individual are similar under different conditions. Test-retest comparisons are the most appropriate method for assessing reliability if the instrument is intended as an evaluative tool. Reliability can also be assessed using internal consistency; this checks the extent to which similar questions give consistent replies.[10]

Responsiveness considers whether the tool is sensitive to assess measurable change. If meaningful comparisons are to be made then a standardized measure of responsiveness is required. The standardized response mean allows such a comparison (this represents the mean change in score over two points in time divided by the standard deviation of the score differences).[11]

SYSTEM-SPECIFIC QUESTIONNAIRES

Correct and consistent clinical diagnosis and subsequent classification are vital before addressing the post-treatment phase with disease-specific questionnaires. The CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) classification was developed in 1994 and was translated into several languages and adopted worldwide by the vascular community.

The CEAP system, however, is not easily translated into a quantifiable scoring system; for this a Venous Clinical Severity Score (VCSS) and a Venous Segmental Disease Score (VSDS) was proposed.[12] In summary the VCSS grades 10 clinical characteristics from absent to severe (see Table 34.1). The VSDS assesses the anatomical and pathophysiological characteristics of CEAP. The scores are allocated to 11 venous segments with reflux and/or obstruction based on venous imaging. In addition a Venous Disability Score (VDS) has been published with the intention of measuring the degree of impairment in daily activities.

To allow the comparison of different treatments or results from different publications there is a need for standardization of the severity of the venous disease being studied. These scoring systems are an adjunct to the current armamentarium and are to be recommended for use in future venous outcome assessment studies. These studies are as yet to be applied to a large multicenter study of patients with varicose veins.

Currently there are three system- or disease-specific instruments for measurement of health-related quality of life in patients with chronic venous disease of the lower limb that can be applied to patients with varicose veins (see Table 34.2).

Disease-Specific Studies

Aberdeen Varicose Vein Score

This initially was designed as a postal questionnaire. Published in 1993, it surveyed 373 patients with varicose veins selected from a hospital and general practice setting. A comparison group was made up of a random sample of 900 members of the general population selected from the electoral register of Aberdeen. They were sent a similar questionnaire without the condition-specific tool. The validity of the questionnaire was shown by a high correlation with the SF-36 health profile; the perceived health of patients with varicose veins was significantly lower than that of the general population.[13]

In 1999 the Aberdeen Varicose Vein questionnaire (AVVQ) was used to determine the quality of life of patients with varicose veins both before and after surgery.[16] This was a prospective consecutive cohort of 137 patients with primary varicose veins (recurrent veins, deep venous disease, and an

TABLE 34.2 Disease-Specific Studies on the Quality of Life in Patients with Chronic Venous Disease

Name and year	Language	Patients evaluated	Summary
Aberdeen Varicose Vein Questionnaire (AVVQ) 1993[13]	English	Varicose veins and chronic venous disease	Grid used to score the extent of the varicosities
Chronic Venous Insufficiency Questionnaire (CIVIQ) 1996[14]	English French	Chronic venous disease	Clinical and subjective symptoms used
Venous Insufficiency Epidemiological and Economic Study (VEINES) 2003[15]	English French French Canadian Italian	Chronic venous disease	Large patient database, assesses C1–C6 disease (CEAP)

TABLE 34.3 Aberdeen Varicose Vein Symptom Severity Scores (AVVSSS) in Patients with Primary Varicose Veins Pre- and Postsurgery

Symptom severity score	Median score	Interquartile ranges	Significance (compared with baseline scores)
Presurgery	17.7	11.8–27.2	
4 weeks postsurgery	13.8	7.9–21.3	Not significant
6 months postsurgery	9.6	4.2–15.8	$P < 0.001$
2 years postsurgery	8.1	4.0–14.7	$P < 0.001$

ulcer history were excluded). Patients completed the SF-36, the Aberdeen questionnaire, and a set of 25 questions focussing on the symptoms and concerns. The conclusion was that the AVVQ was a valid measure of quality of life for patients pre- and postsurgery. Patients were found to have a significantly improved quality of life six weeks postsurgery.

Two studies emerged in 2002 where the AVVQ was used. In a prospective study of 203 unselected patients with CEAP 2–6 who underwent saphenous vein surgery (with or without subfascial endoscopic perforator surgery) for primary and recurrent disease there was an improvement in disease-specific quality of life at six months and at two years (86% and 87% of patients, respectively). Also the higher the AVVQ severity score (the worse the symptoms) before surgery, the greater the improvement seen at two years (see Table 34.3).[17]

Another study looked at the effect of stripping on health-related quality of life. A prospective study recruited 66 patients who underwent varicose vein surgery with attempted stripping of the long saphenous vein (LSV) to the knee. The AVVQ and SF-36 were used to assess outcome. LSV surgery led to a significant improvement in disease-specific health-related quality of life for up to two years. In patients with no deep venous reflux, stripping of the LSV to the knee gave additional benefit. The effect of surgery on generic quality of life was demonstrated only in bodily pain; patients who underwent stripping of the LSV had a significantly better score at two years.[18]

Chronic Venous Insufficiency Questionnaire (CIVIQ)

This questionnaire was developed from a patient database of over 2000 subjects and was described both in French and English. The first version of the CIVIQ was tested in a cross-sectional observational study on subjects recruited by general practitioners, divided into those with and without venous insufficiency. The diagnosis was made on clinical and subjective symptoms. A second analysis (CIVIQ 2) was performed using a questionnaire with a total of 20 equally weighted items on the 1001 patients with chronic venous disease based on four criteria: physical, psychological, social, and pain. Subsequent to this CIVIQ was used in a randomized, double-blind trial on 934 patients to compare two formulations of a drug (a flavonoid) in patients with chronic venous symptoms.

The conclusions were that the specific quality of life questionnaire for chronic lower limb venous insufficiency was appropriate, reliable, and specific.[14] It is notable however, that this questionnaire has not been used in subsequent trials to assess quality of life in patients with chronic venous insufficiency.

Venous Insufficiency Epidemiological and Economic Study (VEINES)

The VEINES study was an international, prospective cohort study that evaluated epidemiology (natural history and risk factors) and outcomes (clinical outcomes, quality of life, costs, health service use) in chronic venous disease. The VEINES sample represented approximately 10 years of data and was a prospective registration of 5688 outpatients with chronic venous disease.

In 1998 the development and psychometric evaluation of the questionnaire was described measuring quality of life and symptoms (VEINES-QoL and VEINES-SYM). The 26-item questionnaire included categories on chronic venous

disorders of the leg (telangiectasia, varicose veins, edema, skin changes, and leg ulcers), psychological factors, and items regarding change over time. There were four language versions and it was assessed initially in 615 patients. The results confirmed that the questionnaire was acceptable, reliable, and had good validity and responsiveness in all four languages in European and North American populations.[19] Construct validity also was demonstrated in comparisons between multiple languages with the SF-36 and with CEAP classifications.

In 2001 a VEINES study of 1313 patients concluded that findings concerning quality of life in patients with varicose veins could only be reliably interpreted when concomitant venous disease was taken into account. In patients with varicose veins alone the objectives of cosmetic improvement and the improvement in quality of life should be considered separately. VEINES-QoL was more sensitive to the combination of venous disorders with varicose veins than those provided by the SF-36.[20]

The relationship between CEAP classification and patient-perceived quality of life was evaluated in 2005. The VEINES cohort of patients was used and it was found that CEAP class was significantly associated with generic and disease-specific quality of life. CEAP class predicted disease-specific but not generic quality of life scores; higher CEAP class was associated with poorer disease-specific quality of life. This study also provided further evidence of the validity of the VEINES-QoL and VEINES-SYM and the specificity of CEAP in detecting morbidity attributable to chronic venous diseases.[21]

PROBLEMS

There is a dearth of published data on quality of life assessments in patients with varicose veins despite the large number of operations performed each year. There are also a plethora of techniques now available for the treatment of varicose veins, yet no assessment with either generic or disease-specific tools.

The possible reasons for the paucity of publications may be that this research modality is time consuming and the response rate from the subjects is often poor. Pressure from a patient-centered National Health Service and National Institute for Clinical Excellence (NICE) will change this. In two recent large multicenter national trials, the United Kingdom small aneurysm trial (UKSAT) and endovascular aneurysm repair trial (EVAR 1) both used quality of life tools in their assessment along with the more familiar morbidity and mortality data.[22,23]

In the forum of innovative therapies for varicose veins, new techniques will have to undergo rigorous testing and will have to demonstrate that they are of benefit before funding is approved; quality of life tools will be paramount in this.

CONCLUSION

The AVVS was one of the first tools to evaluate a surgical intervention for venous insufficiency. It is unique in visually scoring the extent of varicose veins with a pictorial representation of each patient's varicose veins on a standardized grid. The AVVS demonstrated that patients with the worst scores had the most to gain from surgery. It may be that AVVS could be used as a prescoring technique to quantify the severity of disease present and thereby be used as a means of identifying the patients whose treatment could be deemed to be the most cost effective.

Each disease-specific instrument asks about pain, appearance, and immobility. CIVIQ and VEINES are large multinational instruments that have been shown to be useful in investigating the lower (less severe) CEAP classes.

At present there is no single quality of life tool that can be used to measure the impact of venous disorders on patients. The use of psychometric tools is paramount to the measurement of surgical outcomes and is intertwined with future funding of new techniques for venous disease. Quality of life should be a standard measure in future studies in assessing treatments for venous diseases, preferably with a combination of generic and disease-specific tools. Following the introduction of a new treatment there is a need for valid and reliable measures of health outcome in order for limited resources to be best allocated in the most cost-effective manner. The disease-specific questionnaires described earlier are validated, reliable tools, and their use in future trials is mandatory in conjunction with generic studies in order to evaluate the impact of new therapies on patients with varicose veins.

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CHAPTER

35

Pelvic Congestion Syndrome: Diagnosis and Treatment

GRAEME RICHARDSON

INTRODUCTION

Pelvic congestion syndrome (PCS) is still treated with skepticism by the medical community, yet in most instances it could be called the female varicocele, and is the female version of male varicocele which is well recognized.

PCS is a distinct clinical entity in relatively young multiparous women characterized by chronic pelvic pain in the setting of pelvic venous varicosities. The syndrome, first described as a vascular condition by Taylor in 1949,[1] was more recently shown by Hobbs[2] to be the result of venous engorgement of the pelvis due to gross dilatation and incompetence of one or both of the ovarian veins. In a series of 50 symptomatic patients with either pelvic or vulval varicose veins assessed by our ultrasound techniques in Wagga Wagga, the cause was found to be ovarian vein reflux in 71% of cases, more often the left than the right (24:9). These cases could well be described as the female varicocele. Saphenofemoral tributaries were the only cause of vulval varicose veins in approximately 10% of cases, and the remainder were assumed to be caused by internal iliac reflux alone. The latter probably accounts for at least 10% of the cases of pelvic congestion syndrome. In addition, it seems likely that segmental pelvic vein reflux accounts for a further 10% of cases. Many patients with recurrent leg varicose veins are found to have a significant component of their problem from the pelvis. Seeking symptoms of PCS, a history of vulval varicose veins of pregnancy, and looking for a contribution from the pelvis in all patients presenting with leg varicosities will result in a greater awareness of a common yet poorly understood clinical problem.

ETIOLOGY

Although rarely seen in nulliparous teenagers and young women, when one may assume the cause is identical to male varicocele, this condition largely follows pregnancy. Vulval varicose veins are said to occur in 2 to 7% of pregnancies.[3,4] These become larger in subsequent pregnancies, although they often disappear in the postpartum period. Usually after three pregnancies some varicose veins remain in the vulva, upper medial thigh, perianal, or gluteal regions. Probably the majority of cases are related to massive enlargement of the ovarian veins draining the pregnant uterus, perhaps associated with internal iliac vein compression. Perhaps after pregnancy some ovarian veins do not return to normal size, and the limited one or two valves at the upper end of the ovarian veins may become incompetent. Maybe segmental reflux occurs in tributaries of the internal iliac veins such as the uterine veins, and the round ligament veins, and can be responsible for persisting pelvic varicosities, even though we are unable to demonstrate ovarian vein or main trunk internal iliac vein reflux. We have often demonstrated this segmental reflux in our pelvic ultrasound assessment.

Compression syndromes are a further cause of left ovarian vein reflux, particularly superior mesenteric artery compression of the left renal vein and retroaortic left renal vein with compression. Compression of the left common iliac vein by the right common iliac artery can produce internal iliac reflux.

Although hormonal and psychiatric factors have at times been implicated in the symptomatology, exacerbation of symptoms with menstruation, sexual activity, and ovulation

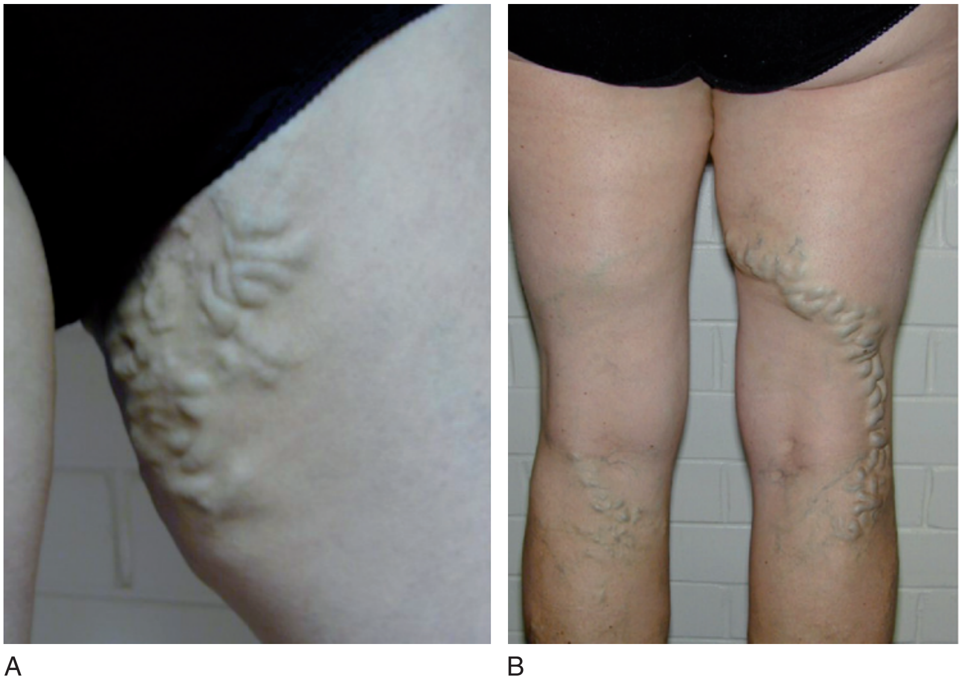


FIGURE 35.1 **A**. Residual vulval varices. **B**. Vulval to posterior thigh to lateral calf varices.

suggests increased arterial flow to the pelvis at these times results in pooling of venous blood in the pelvic varicosities. This results in pressure in the pelvis alone, or if there are pelvic escape veins some or all of the pressure is transmitted to the vulva, buttock, or leg varicosities.

If large pelvic veins persist in the broad ligament, typical pelvic symptoms occur. Associated with these varicosities there may be pelvic escape through either the internal iliac tributaries, namely obturator or internal pudendal, or the round ligament into the vulva and upper medial thigh, or posteriorly into the buttock and posterior thigh (see Figure 35.1A), sometimes including varices of the vein of the sciatic nerve producing sciatica. These veins usually feed into either the long or short saphenous system, and if these are not treated at the time of treatment of long or short saphenous varicose veins, then they cause recurrent varicose veins. A typical pattern is posterior vulval veins coursing posteriorly into the short saphenous via the Giacomini vein (see Figure 35.1B).

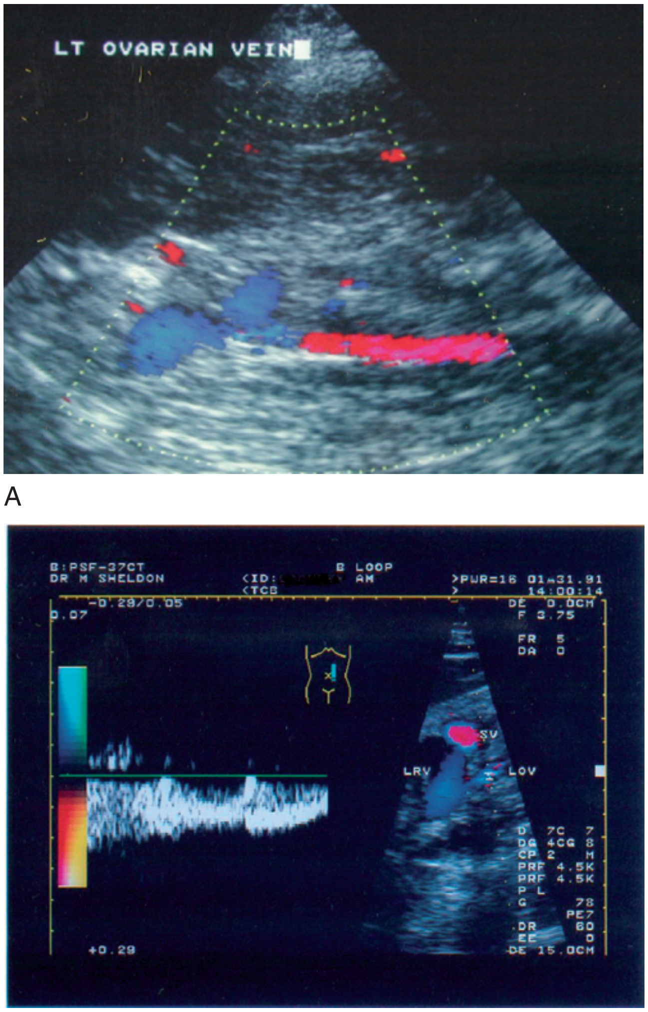
DIAGNOSIS

Clinical suspicion of PCS relies on typical symptoms, namely pelvic heaviness or deep pelvic pain, which is present before the menstrual period and on day 1 and sometimes day 2 of menstruation, mid-cycle, and post-coital. The latter is particularly noticeable on standing up immediately after having had morning intercourse. This aching may persist for several hours through the day. The pelvic heaviness is particularly severe after long periods of standing. Many patients complain of dyspareunia and many are aware of vulval and leg varicosities, which are worse at the time of their pelvic symptoms. Commonly there are bladder symptoms related to perivesical varicosities causing frequency or a difficulty in starting the flow of urine. Many patients have symptoms of irritable bowel syndrome.

The diagnosis of PCS is often delayed until investigations looking for endometriosis, inflammatory bowel disease, urinary tract disease, or pelvic inflammatory disease have proved negative. It is common for patients to have suffered marital stress and dissatisfaction with their treating doctor's lack of interest in their condition.

INVESTIGATIONS

All patients with symptoms consistent with PCS are examined carefully to exclude other causes of pelvic pathology, and then undergo standard pelvic ultrasound and duplex ultrasound assessment of the pelvic, ovarian, and when appropriate, groin and lower limb veins. Earlier reports have advocated venography to demonstrate pelvic varices, either by use of vulval varicography,[5] transuterine,[6,7] per-osseous[8] venography, or selective ovarian venography.[9,10] These techniques are invasive and may, in some cases, invalidate assessment for reflux. For example, if a catheter is placed selectively adjacent to or inside the orifice of the right or left ovarian vein, it may pass the only valve present, and injection will then



A

B

FIGURE 35.2 **A**. Ultrasound left ovarian vein (red) and left renal vein (blue). **B**. U/S left ovarian vein/LRV with waveform showing reflux.

demonstrate apparent reflux. Varicography can demonstrate the anatomy of vulval and buttock varices and the relevant pelvic escape veins, but not the physiology, for example, reflux (see Figure 35.3). More recently, MRI and multislice CT have been used to detect pelvic varices[11] in the assessment of chronic pelvic pain. Dynamic MRI techniques currently are being developed in Madrid (personal communication) that can show ovarian vein reflux, but will need to be compared with ultrasound techniques for cost and reliability.

Ultrasound Assessment

PCS is confirmed on transvaginal ultrasound by finding excessive pelvic varicose veins in the broad ligament, which we would grade as mild (<5 mm), moderate (5–7 mm), or marked (8–10 mm), depending on the diameter, and whether these pelvic varicosities are found to distend when the patient is tilted head up by 60° on a motorized ultrasound examination table. Our ultrasound assessment begins with the patient presenting after six hours of fasting, with a full bladder. Fasting reduces gut motility, and the full bladder enables standard gynecological pelvic ultrasound. A full bladder, however, compresses pelvic varicosities, which may be visible by transabdominal ultrasound after voiding. Transvaginal ultrasound then follows, and having confirmed PCS, we examine the ovarian veins and the internal iliac veins, including anterior and posterior divisions. The round ligament veins and saphenofemoral tributaries also are assessed.

In Wagga Wagga, windows were developed to assess ovarian vein incompetence using transabdominal duplex ultrasound and color flow Doppler (3.5 or 5 MHz transducer).[12] We demonstrated the ability to locate ovarian veins and assess reflux in 93% of cases,[13] which compares well with the 92% visualization shown by Lechter using venography. The left ovarian vein is found by first locating the left renal vein as it passes under the superior mesenteric artery. The ultrasound window is through the left lobe of the liver and the pancreas. The ovarian vein is located by following the left renal vein laterally and rotating the transducer through 90 degrees (see Figure 35.2A). A retroaortic left renal vein, duplicated renal vein, or large ureteric veins are noted if present. It is important to not confuse accessory renal veins or the inferior mesenteric vein for the ovarian vein. The right ovarian vein is found using a window through the liver or gallbladder, by following the inferior vena cava upward to where the right ovarian vein enters it anterolaterally at a very acute angle. Sampling by color and waveform is taken about 2 cm below the termination of the ovarian veins (see Figure 35.2B). The criterion for incompetence in the ovarian vein is reversed flow when lying, sitting, or standing without augmentation. Treatment either by surgery, or more recently endovascular methods, is based on the ultrasound findings.

Laparoscopy

Laparoscopy sometimes is required to exclude other possible causes for pelvic pain, such as endometriosis or pelvic inflammatory disease in patients who have pelvic varices on ultrasound assessment. We do this with the patient's gynecologist. Laparoscopy involves using an extra left iliac fossa port to retract the sigmoid colon. The patient, who initially is head down for gynecological laparoscopy, is then tilted head up and the ovarian and broad ligament veins are seen to distend rapidly if reflux is present.

Venography

Many centers rely on clinical findings, then proceed to selective venography for confirmation, and then to endovascular treatment. Ultrasound confirmation of excessive pelvic varicose veins by transvaginal ultrasound, even if ultrasound

FIGURE 35.3 Varicogram vulval varices with round ligament and obturator pelvic escape veins.

assessment for ovarian vein reflux is not possible, should prevent unnecessary invasive venography, and assist in provision of informed consent, should a patient be referred to an interventional radiologist for venography with a view to coils +/– sclerotherapy. Left renal venography is followed by selective ovarian venography (see Figures 35.4 and 35.5). If indicated by ultrasound findings, we may do selective iliac venograms.

TREATMENT

Various methods have been used to treat the symptoms of pelvic congestion, including psychotherapy, ovarian suppression,[14] intravenous dihydroergotamine,[15] and bilateral oophorectomy with hysterectomy.[16] Ovarian vein ligation has been performed to eliminate reflux since 1985, as either a bilateral procedure,[17] or unilateral based on ultrasound assessment (Richardson 1989). The long-term results of such treatment have been poorly investigated. It is important that any assessment of treatment of venous conditions needs to have at least five-year follow-up. Of recent years, however, endovascular ablative techniques have been popularized, and again need to be adequately assessed.

As many of these patients have associated leg varicosities, a treatment plan is required. The pelvic veins are treated only if there are pelvic symptoms, or if they significantly contribute to the leg varicosities. In these cases the pelvic veins are treated initially, and the response of symptoms is determined over a period of two to three months before treating the vulval or leg varicosities. In a few instances, the veins can reduce in size such that sclerotherapy of the residual vulval or leg veins might be appropriate, rather than surgical treatment.

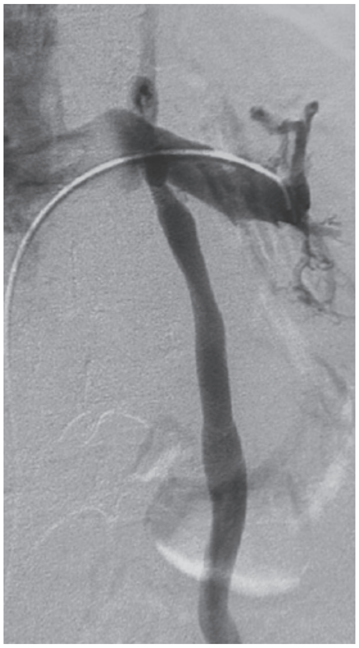


FIGURE 35.4 Left renal venogram with reflux into large LOV. Note the narrow upper end, which helps prevent embolization of coils.

Ovarian Vein Incompetence

As most cases involve treatment of the left ovarian vein, the choice of treatment is between operation and endovascular ablation techniques. Laparoscopic treatment has been investigated, and although it is possible to clip the upper end of the ovarian veins, it is currently not possible to remove a segment, nor would it be easy to deal with nearby tributaries.

Operation

Ovarian vein ligation has been performed on 120 patients since 1989 by the author. It involves a *sympathectomy* incision with a muscle splitting extraperitoneal approach to the ureter and the adjacent ovarian vein, which is ligated carefully using nonabsorbable material at the level of the pelvic brim. The ligature is then used for traction to enable further multiple ligations upward to finish at approximately 2 cm from the left renal vein. A narrow Dever retractor is useful

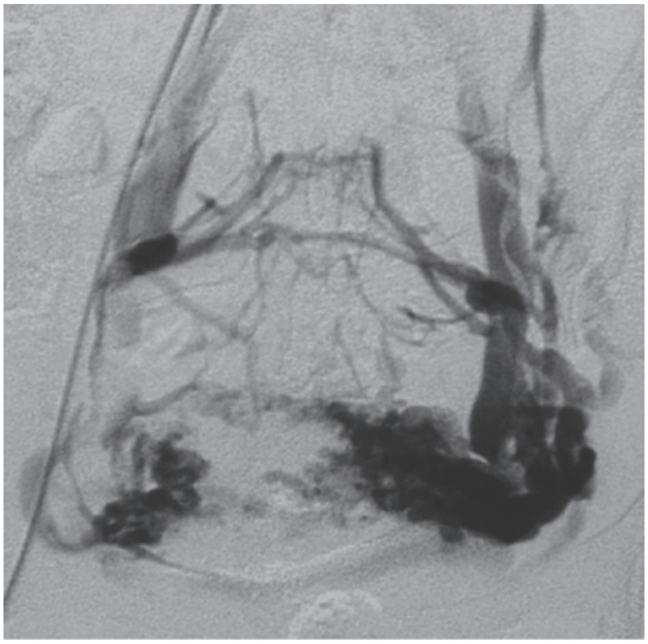


FIGURE 35.5 Selective left ovarian venogram filling large left broad ligament varices with crossover to the right broad ligament and drainage via the ROV and both iliac veins, also showing presacral veins.

to expose this uppermost portion. There is significant risk of major hemorrhage if the ovarian vein is not handled gently. Operation requires approximately two days hospitalization and two weeks discomfort, which for a mother of young children is a considerable inconvenience compared with outpatient endovascular treatment. When choosing the most appropriate method of ovarian vein ablation, we accept that surgical ligation is complete, and provided all tributaries have been ligated, should produce long-term ablation of the ovarian vein. It can be performed by any general surgeon and requires no special equipment. It does produce a scar, however, and discomfort. I should reiterate that I would ligate only an ovarian vein that was shown to reflux on ultrasound assessment. Other surgeons have routinely ligated both ovarian veins.[2,17] It would seem unwise to ligate a draining vein that did not reflux. Some surgeons have advocated an even more extensive dissection to include the ovarian pedicle.[18] There is no evidence to suggest a more limited operation such as the Wagga Wagga technique has inferior results.

Surgical Results

Long-term results in a series of 72 patients treated until June 1995 in Wagga Wagga certainly encourages one to treat patients based on the ultrasound findings of ovarian vein reflux.[19] These patients were sent questionnaires and were assessed independently by a surgical registrar for their quantitative response of symptoms to surgical treatment using visual analogue scales.[20] Sixty-seven of the 72 patients responded with a mean follow-up of 33 months (range 4 to 71) with a mean age of 35 years and mean pregnancies of 3.1. Pelvic heaviness was found to improve significantly (>50%) in 70% of patients, and in 56% of patients, this was almost complete. Thirteen percent reported little or no improvement, and when these were subsequently investigated, including further ultrasound and venography, no ovarian reflux could be found, and in all cases alternative diagnoses such as irritable bowel syndrome were present. Dyspareunia was present preoperatively in 82% of cases, and 84% of these improved, 50% of these patients reported complete recovery.

Post-intercourse pelvic aching was present in 75% of patients, and improved in 70% of cases with 64% having complete recovery. Bladder symptoms of frequency and obstruction improved in 45% of patients, and some of the 20% of patients who preoperatively were aware of bowel spasm improved. Two patients had normal pregnancies subsequent to ovarian vein ligation with no development of vulval veins in the pregnancy and no recurrence of symptoms.

Ovarian Endovascular Ablation

There have been several reports of single or a few case reports of successful treatment by ovarian vein embolization.[21–24] Thus far, there has been no standardization of the techniques used by several centers but, in all instances, coils of various diameters and lengths have been used. In some centers, sclerotherapy has been used but in the Dutch[23] experience, sclerotherapy was contraindicated because of a perceived risk of entering the portal system. A team in Vancouver, which has a very large experience of treatment of male varicocele using similar techniques has utilized a combination of coils and glue (personal communication).

Since January 1999 we have been using endovascular techniques. We prefer to use an inguinal approach, and when cannulation of the ovarian vein is difficult, would use a guiding catheter and still use the groin, rather than a jugular or brachial approach. Our technique uses stainless steel coils with attached synthetic fibers (Cook), choosing a diameter to oversize by 2 to 3 mm the ovarian vein diameter. In addition, sclerosant has been used with 2 ml of 3% Aethoxysklerol diluted with about 1 to 2 ml of contrast so that the spread of sclerosant can be seen clearly on the screen to avoid spillover into the left renal vein. Air is added and the syringe shaken to produce coarse bubbles. Our hope is that the sclerosant will help obliterate pelvic and broad ligament varices. By causing spasm we may help prevent migration of the coils. In no instances have we seen any contrast pass beyond the ovarian vein or broad ligament veins. Although preparing the sclerosant as a foam would seem desirable, the

contrast is further diluted and less visible than with coarse bubbles, and we are less sure of its spread. In an attempt to reduce the cost to the patient we have tried to use the minimum number of coils to achieve the following principles. The first coil is deployed at the level of the pelvic brim just above where it crosses the ureter. Depending on the anatomy of the ovarian vein, we aim to place a coil across junctions or selectively coil major tributaries. We try to have good cross-section coverage of the vein by varying the deployment, and we aim to have the highest point above all incompetent tributaries, and within 2 to 3 cm of the left renal vein. Usually two long (20 cm) coils suffice, with occasional shorter coils in tributaries or at the upper end of the vein. We are aiming for the highest and longest possible ablation.

Our approach has been via the right femoral vein and having confirmed ovarian vein reflux by a selective left renal venogram, a guidewire is passed down the ovarian vein to the pelvis, and a catheter advanced to the level of the pelvic brim. Approximately one-third of the 2 ml of sclerosant is injected slowly, with the patient holding her breath with Valsalva as long as possible. In male varicocele patients, this is combined with compression at the level of the external ring to avoid the sclerosant passing into the scrotum.

There are risks to endovascular techniques including embolization, migration and perforation of coils, irritation of nerves such as genitofemoral, and the possibility of late recanalization. There have been reports of recanalization resulting in recurrent symptoms requiring later surgical treatment.

Internal Iliac Veins

Where patients are shown to have significant internal iliac vein reflux as a cause for the pelvic congestion syndrome, surgical treatment to ligate the main branch or selectively the anterior division has been performed on a few patients in our series and by others.[18] There are risks to the surrounding structures, such as ureter and iliac vessels. There are also significant risks to endovascular treatment of the internal iliac system, being a very large vein at its junction with the external iliac vein. The shape of the vein encourages embolization. In one case, we have deployed a coil into the anterior division together with sclerotherapy. When the patient has ovarian and internal iliac vein reflux on ultrasound assessment, we have treated only the ovarian vein. Thus far we have not needed to treat the internal iliac vein because of a disappointing result.

Vulval Varicosities

Having treated the ovarian vein, these improve and can be treated by avulsion techniques by minor surgery, or at the time of dealing with the long or short saphenous varicosities. Large round ligament veins can be ligated as they emerge from the external inguinal ring. Sclerotherapy of residual minor vulval varicosities is possible, and the author on many occasions has used 2%Aethoxysklerol. To apply adequate compression after the sclerotherapy I use cotton balls covered by tape and the patient wears a firm support, such as bicycle pants, in an attempt to provide as much compression as practical. Side effects from the sclerotherapy have been surprisingly few.

Ureteric Vein Reflux

Inevitably unusual cases will appear associated with venous anomalies. We have treated several cases with large refluxing ureteric veins that are tortuous and feed into the ovarian vein usually in the lower third of the abdomen. They are often difficult to cannulate for coil treatment. Sometimes the ovarian vein joins a lower renal vein branch, or a large lumbar vein rather than the renal vein, and sometimes the ovarian or the renal vein is duplicated. In all cases coming to endovascular treatment we have to be prepared for such anomalies and devise the best treatment strategy.

Other Causes of Pelvic Congestion

Some patients present with congestion symptoms or minor vulval varices, yet we are unable to demonstrate ovarian or internal iliac incompetence. As with most venous disease, there is variability related to long periods of standing and the menstrual cycle. Repeat ultrasound studies show this and we try to perform studies when symptoms are maximal. There remain patients where there clearly are significant pelvic varices but no source of reflux. Some of these are due to venous obstruction associated with collateral venous pathways. We have observed patients with both fixed and intermittent reflux of internal iliac veins associated with common iliac vein obstruction. In some cases this is postural, when recumbent there is reversed flow, and is associated with 1 to 2 mm AP diameter where the right common iliac artery crosses the left common iliac vein. Perhaps some of these patients would benefit from a venous stent. A retroaortic left renal vein frequently has been associated with PCS and rarely left renal vein obstruction following surgical ligation. I avoid ablation of the ovarian vein in these patients with collateral drainage of the kidney.

Segmental Pelvic Vein Reflux

There remains a group of patients where we cannot demonstrate a definite cause. It appears quite feasible that some very large pelvic veins in pregnancy don't shrink and produce segmental reflux in uterine and broad ligament veins. These patients and others whose symptoms fail to resolve

after ovarian or iliac vein ablation are best treated by hysterectomy.

COMPARISON OF RESULTS OF COIL AND SURGICAL TREATMENT OF OVARIAN REFLUX

Patients treated by surgery from 1989 until 1998, and endovascular treatment from 1999 until June 2002 were studied using a questionnaire with visual analog scales. Statistical analysis of pelvic heaviness and overall satisfaction showed no difference between endovascular and surgical treatment.[25] Both treatments resulted in statistically significant improvement after treatment. A decision to treat in both groups was based on clinical findings and ultrasound assessment, and there was no statistical difference in the presenting features of patients in either the surgical or the endovascular series.

Patients undergoing coil treatment were also subjected to follow-up ultrasound studies at six weeks–six months and also abdominal radiographs. There was no evidence of coil migration in 34 patients. Early ultrasounds showed two clots in broad ligament veins, no significant reduction in diameter at six to 10 weeks, but some evidence of reduction by six months.

Long-term results of endovascular treatment have not yet been reported. Re-canalization remains possible but should be amenable to further endovascular treatment. Although the great majority of patients tolerate coil treatment with little discomfort, anxious patients are more difficult to cannulate the femoral vein, and spasm of the ovarian vein could lead to perforation. Patients have far less loin discomfort than after surgery, but it seems excessive exercise should be restricted. A few patients have severe pain and this could be due to thrombosis of the ovarian vein or perforation.

Patient satisfaction justifies ablation of an ovarian vein shown by ultrasound to reflux.

Provided endovascular ovarian vein ablation can be delivered safely and at reasonable cost, then there are definite advantages over surgical treatment. Complications can occur from either method. The incidence of long-term recanalization is unknown.

There is no evidence that endovascular treatment produces better results than surgery. Provided patients are prepared to accept the scar, pain, hospitalization, and other potential complications of an operation, at this point one cannot say surgical treatment has been superseded.

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CHAPTER

36

The Epidemiology of Venous Thromboembolism in the Community: Implications for Prevention and Management

JOHN A. HEIT

INTRODUCTION

The epidemiology of venous thromboembolism (VTE) in the community has important implications for VTE prevention and management. This chapter describes the incidence, survival, recurrence, complications, and risk factors for deep vein thrombosis of the leg, pelvis, or arm, and its complication, pulmonary embolism. The epidemiology of thrombosis affecting other venous circulations (e.g., cerebral sinus, mesenteric, renal, hepatic, portal) is beyond the scope of this review. Since population-based studies of venous thromboembolism epidemiology are most generalizeable to the reader's individual patients, this chapter focuses on data provided from studies that included the complete spectrum of the disease from well-described populations.

THE INCIDENCE OF DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

The average annual incidence rates of venous thromboembolism among white Americans during the 25-year period, 1966 to 1990 (age- and sex-adjusted to the 1980 U.S. white population), was 117 per 100,000 person-years.[1] The venous thromboembolism incidence over the more recent seven-year period, 1991 to 1997 (117.7 per 100,000; similarly adjusted, but to the 2000 U.S. white population), has not changed significantly compared to the 10-year period, 1981 to 1990 (116.7 per 100,000; see Figure 36.1). Based on the more recent rates, 249,000 incident venous thromboembolism cases occur annually among U.S. whites. The incidence appears to be similar or higher among African-Americans and lower among Asian- and Native-Americans.[2–6] Assuming that the 1991 to 1997 age- and sex-specific venous thromboembolism incidence among blacks (black- or African-American alone) is comparable to whites, and adjusting for the different age and sex distribution of black-Americans, the overall age- and sex-adjusted venous thromboembolism incidence was 77.6 per 100,000. Based on this incidence, 27,000 incident venous thromboembolism cases occur annually among U.S. blacks, for a total of over 275,000 new venous thromboembolism cases per year in the United States.

Venous thromboembolism is predominantly a disease of older age.[1,7,8] In the absence of a central venous catheter[9] or thrombophilia,[10] venous thromboembolism is rare prior to late adolescence.[1,11] The age- and sex-adjusted venous thromboembolism incidence rate for persons age 15 years or older is 149 per 100,000.[1] Incidence rates increase exponentially with age for both men and women and for both deep vein thrombosis and pulmonary embolism (see Figures 36.2 and 36.3).[1,8] The overall age-adjusted incidence rate is higher for men (130 per 100,000) than women (110 per 100,000; male : female sex ratio is 1.2 : 1).[1] Incidence rates are somewhat higher in women during the childbearing years, whereas incidence rates after age 45 years are generally higher in men. Pulmonary embolism accounts for an increasing proportion of venous thromboembolism with increasing age for both genders.[1]

SURVIVAL AFTER DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Survival after venous thromboembolism is worse than expected, and survival after pulmonary embolism is much worse than after deep vein thrombosis alone (see

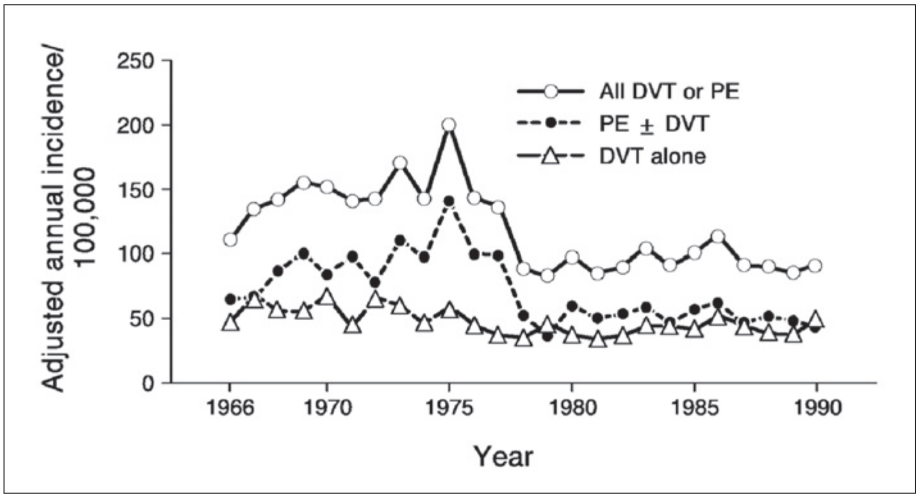

FIGURE 36.1 Age- and sex-adjusted annual incidence of all venous thromboembolism, deep vein thrombosis (DVT) alone, and pulmonary embolism with or without deep vein thrombosis (PE ± DVT).[1]

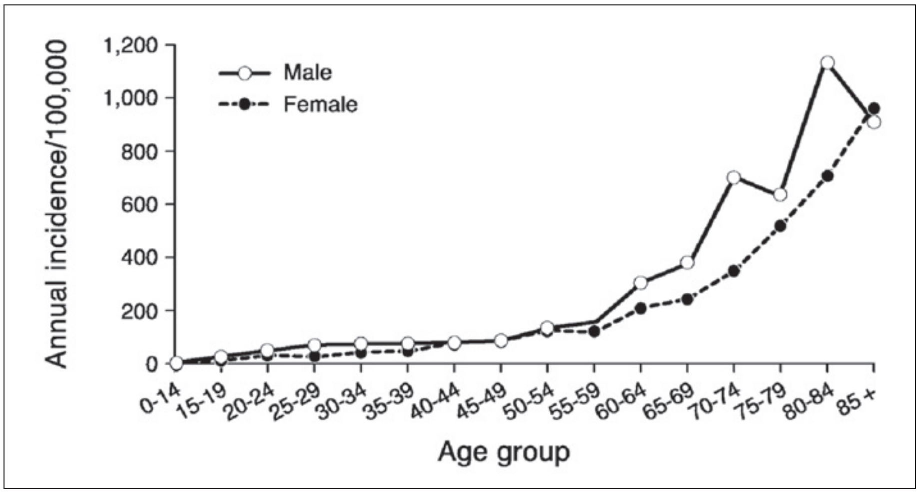

FIGURE 36.2 Annual incidence of venous thromboembolism by age and gender.[1]

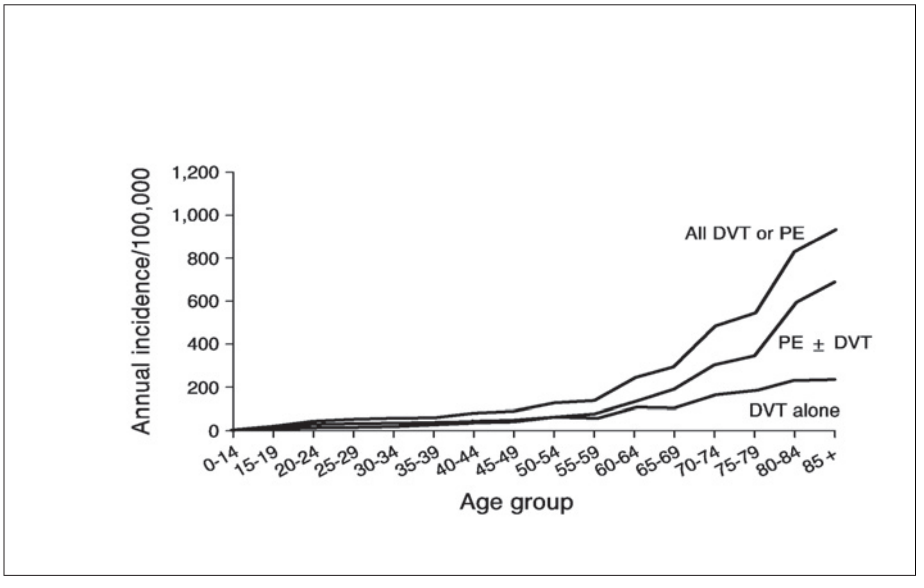

FIGURE 36.3 Annual incidence of all venous thromboembolism, deep vein thrombosis (DVT) alone, and pulmonary embolism with or without deep vein thrombosis (PE ± DVT) by age.[1]

Table 36.1).[12–14] The risk of early death among patients with symptomatic pulmonary embolism is 18-fold higher compared to patients with deep vein thrombosis alone.[12] Pulmonary embolism is an independent predictor of reduced survival for up to three months. For almost one-quarter of pulmonary embolism patients, the initial clinical presentation is sudden death. Independent predictors of reduced early survival after venous thromboembolism include increasing age, male gender, lower body mass index, confinement to a hospital or nursing home at venous thromboembolism onset, congestive heart failure, chronic lung disease, serious neurological disease, and active malignancy.[8,12,13] Additional clinical predictors of poor early survival after pulmonary embolism include syncope and arterial hypotension.[15] Evidence of right heart failure based on clinical examination, plasma markers (e.g., cardiac troponin T, brain natriuretic peptide)[16,17] or echocardiography[13] predicts poor survival among normotensive pulmonary embolism patients. Pulmonary embolism patients with these characteristics should receive aggressive anticoagulation therapy, and possibly thrombolytic therapy in selected cases.[18,19]

TABLE 36.1 Survival (%) After Deep Vein Thrombosis vs. Pulmonary Embolism[12]

Time	Deep vein thrombosis alone	Pulmonary embolism
0 days	97.0	76.5
7 days	96.2	71.1
14 days	95.7	68.7
30 days	94.5	66.8
90 days	91.9	62.8
1 year	85.4	57.4
2 years	81.4	53.6
5 years	72.6	47.4
8 years	65.2	41.5

VENOUS THROMBOEMBOLISM RECURRENCE

Venous thromboembolism recurs frequently; about 30% of patients develop recurrence within the next 10 years (see Table 36.2, Figure 36.4).[20] The hazard of recurrence varies with the time since the incident event and is highest within the first six to 12 months. However, even at 10 years the hazard of recurrent venous thromboembolism never falls to

TABLE 36.2 Cumulative Incidence and Hazard of Venous Thromboembolism Recurrence[20]

Time to recurrence	Venous thromboembolism recurrence: Cumulative recurrence	Hazard of recurrence
	%	*Per 1000 person-days (±SD)*
0 days	0.0	0
7 days	1.6	170 (30)
30 days	5.2	130 (20)
90 days	8.3	30 (5)
180 days	10.1	20 (4)
1 year	12.9	20 (2)
2 years	16.6	10 (1)
5 years	22.8	6 (1)
10 years	30.4	5 (1)

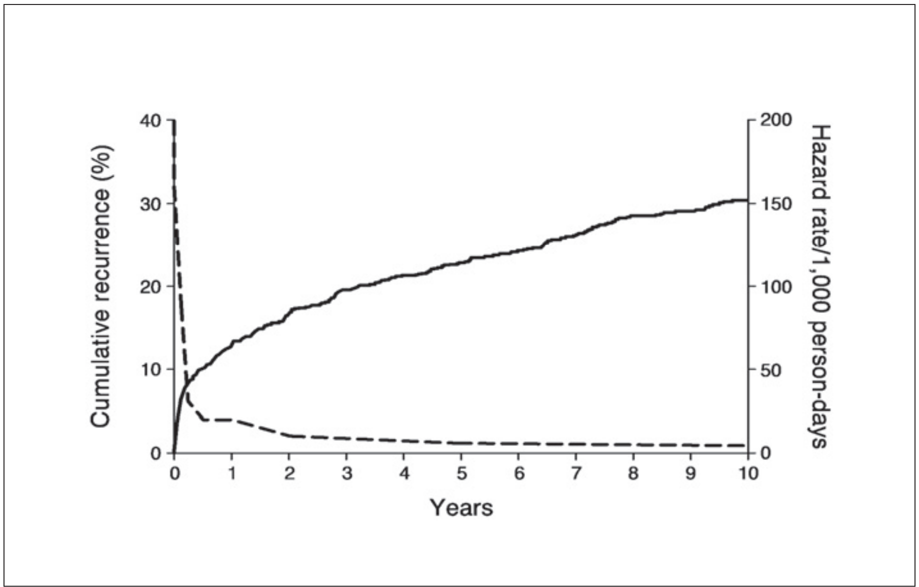

FIGURE 36.4 Cumulative incidence of first venous thromboembolism recurrence (—), and the hazard of first recurrence per 1000 person-days (- - -).[20]

TABLE 36.3 Independent Predictors of Venous Thromboembolism Recurrence[20]

Characteristic	Hazard ratio	95% CI
Age*	1.17	1.11, 1.24
Body Mass Index†	1.24	1.04, 1.47
Neurologic Disease with Extremity Paresis	1.87	1.28, 2.73
Active Malignancy		
Malignancy with Chemotherapy	4.24	2.58, 6.95
Malignancy without Chemotherapy	2.21	1.60, 3.06

*per decade increase in age.
†per 10 kg/m^2 increase in body mass index.

zero. Although active therapeutic anticoagulation is effective in preventing recurrence,[21–23] the duration of anticoagulation does not affect the risk of recurrence once primary therapy for the incident event is stopped.[24–26] These data suggest that for a subset of patients, venous thromboembolism is a chronic disease with episodic recurrence; indefinite secondary prophylaxis may be warranted for this patient subset.[21–23,26,27] Independent predictors of recurrence include male gender,[20,28,29] increasing patient age and body mass index, neurological disease with extremity paresis, and active malignancy (see Table 36.3).[8,20,30–33] Additional predictors include "idiopathic" venous thromboembolism,[22,24,33] a lupus anticoagulant or antiphospholipid antibody,[22,34] antithrombin, protein C or protein S deficiency,[35] and possibly persistent residual deep vein thrombosis.[36] Prolonged secondary prophylaxis with anticoagulation therapy should be considered for patients with these characteristics. Although the incident event type (deep vein thrombosis alone vs. pulmonary embolism) is not a predictor of recurrence, patients with recurrence are significantly more likely to recur with the same event type as the incident event type.[37,38] Because the seven-day case fatality rate is significantly higher for recurrent pulmonary embolism (34%) compared to recurrent deep vein thrombosis alone (4%),[38] prolonged anticoagulation should be considered for incident pulmonary embolism, especially for patients with chronically reduced cardiopulmonary functional reserve.

COMPLICATIONS OF VENOUS THROMBOEMBOLISM

The major complications of venous thromboembolism are venous stasis syndrome (e.g., post-thrombotic syndrome, including dependent leg swelling and pain, stasis pigmentation and dermatitis, and dermatoliposclerosis) and venous ulcer, and chronic thromboembolic pulmonary hypertension. The overall incidence of venous stasis syndrome and venous ulcer is 76.1 and 18.0 per 100,000 person-years, respectively.[39] Venous thromboembolism patients have a 17-fold increased risk of venous stasis syndrome.[39] The 20-year cumulative incidence of venous stasis syndrome after venous thromboembolism and after proximal deep vein thrombosis are about 25% and 40%, respectively.[32,40] Risk factors for venous stasis syndrome include the venous thromboembolism event type (deep vein thrombosis, with our without pulmonary embolism) and deep vein thrombosis location (proximal deep vein thrombosis). The 20-year cumulative incidence of venous ulcer is 3.7%.[40] The risk for venous ulcer is increased 30% per decade of age at the incident venous thromboembolism.[40] Venous thromboembolism accounts for about 12% of all venous stasis syndrome occurring in the community.[39]

The incidence of chronic thromboembolic pulmonary hypertension over the 21-year period, 1976 to 1996, was 6.5 per million person-years.[41] Over this same time period, the incidence of acute pulmonary embolism was 485.6 per million person-years. Thus, the vast majority of acute pulmonary emboli do not progress to chronic thromboembolic pulmonary hypertension. Applying these incidence rates to the 2000 U.S. white population, approximately 1367 new chronic thromboembolic pulmonary hypertension cases occur in the United States annually.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

In order to improve survival, avoid recurrence, prevent complications, and reduce health care costs, the occurrence of venous thromboembolism must be reduced. To reduce venous thromboembolism incidence, persons at risk for venous thromboembolism first must be identified. Independent risk factors for venous thromboembolism include patient age, surgery, trauma, hospital or nursing home confinement, active malignant neoplasm with or without concurrent chemotherapy, central vein catheterization or transvenous pacemaker, prior superficial vein thrombosis, varicose veins among the young, and neurological disease with extremity paresis; patients with chronic liver disease have a reduced risk (see Table 36.4).[42,43] The incidence of VTE increases significantly with age for both idiopathic and secondary VTE, suggesting that the risk associated with advancing age may be due to the biology of aging rather than simply an increased exposure to VTE risk factors with advancing age.[44] Compared to residents in the community, hospitalized residents have over a 150-fold increased incidence of acute venous thromboembolism.[45] Hospitalization and nursing home residents together account for almost 60% of incident venous thromboembolism events occurring in the community.[46] Thus, hospital confinement provides an important opportunity to significantly reduce venous thromboembolism incidence. Of note, hospitalization for medical illness and hospitalization for surgery account for almost

TABLE 36.4 Independent Risk Factors for Deep Vein Thrombosis or Pulmonary Embolism[42]

Baseline characteristic	Odds ratio	95% CI
Institutionalization with or without recent surgery		
Institutionalization without recent surgery	7.98	4.49, 14.18
Institutionalization with recent surgery	21.72	9.44, 49.93
Trauma	12.69	4.06, 39.66
No malignancy	1.0	
Malignancy without chemotherapy	4.05	1.93, 8.52
Malignancy with chemotherapy	6.53	2.11, 20.23
Prior central venous catheter or transvenous pacemaker	5.55	1.57, 19.58
Prior superficial vein thrombosis	4.32	1.76, 10.61
Neurologic disease with extremity paresis	3.04	1.25, 7.38
Serious liver disease	0.10	0.01, 0.71

equal proportions of venous thromboembolism (22% and 24%, respectively), emphasizing the need to provide prophylaxis to both of these risk groups. Nursing home residents independently account for over one-tenth of all venous thromboembolism disease in the community.[46]

The risk among surgery patients can be further stratified based on patient age, type of surgery, and the presence of active cancer.[47,48] The risk of postoperative venous thromboembolism increases with advancing patient age,[49] especially for surgery patients that are 65 years of age or older.[48] High-risk surgical procedures include neurosurgery, major orthopedic surgery of the leg, thoracic, abdominal or pelvic surgery for malignancy, renal transplantation, and cardiovascular surgery.[48] Obesity[49–51] and poor American Society of Anesthesiology physical status[51] are risk factors for venous thromboembolism after total hip arthroplasty. Other independent risk factors for VTE after major surgery (after controlling for active cancer) include intensive care unit (ICU) length of stay greater than six days, immobility, and infection.[49] The risk from surgery may be less with neuraxial (spinal or epidural) anesthesia compared to general anesthesia.[52] Risk factors for VTE among patients hospitalized for acute medical illness may include active cancer and prior VTE.[53] After controlling for active cancer, additional independent risk factors include increasing patient age and body mass index (BMI), prior superficial vein thrombosis, chronic renal disease, neurological disease with extremity paresis, fracture and immobility,[54] and possibly infection.[53]

Active cancer accounts for almost 20% of incident venous thromboembolism events occurring in the community.[46] The risk appears to be higher for patients with pancreatic cancer, lymphoma, malignant brain tumors, cancer of the liver, leukemia, and colorectal and other digestive cancers.[55,56] Cancer patients receiving immunosuppressive or cytotoxic chemotherapy are at even higher risk for venous thromboembolism,[42] including therapy with L-asparaginase, thalidomide, or tamoxifen.

A central venous catheter or transvenous pacemaker now accounts for 9% of incident venous thromboembolism occurring in the community.[46] Prior superficial vein thrombosis is an independent risk factor for subsequent deep vein thrombosis or pulmonary embolism remote from the episode of superficial thrombophlebitis.[42] The risk of deep vein thrombosis imparted by varicose veins is uncertain and appears to vary by patient age.[42] Long haul (>6 hour) air travel is associated with a slightly increased risk for venous thromboembolism that is preventable with elastic stockings.[57] Coenzyme A reductase inhibitor (statin) therapy may provide a 20 to 50% risk reduction for venous thromboembolism.[58] However, the risk associated with atherosclerosis, or other risk factors for atherosclerosis, remains uncertain.[59–61] Body mass index, current or past tobacco smoking, chronic obstructive pulmonary disease, and renal failure are not independent risk factors for venous thromboembolism after controlling for other risk factors (e.g., surgery, hospitalization, trauma).[42] The risk associated with congestive heart failure, independent of hospitalization, is low.[42,43] Among women, additional risk factors for venous thromboembolism include oral contraceptive use and hormone therapy[62] and therapy with the selective estrogen receptor modulator, raloxifene, and pregnancy and the postpartum period.[43,63] Compared to nonpregnant women of childbearing age, the VTE risk among pregnant women is increased over four-fold.[64] The annual VTE incidence is five-fold higher among postpartum compared to pregnant women (511.2 versus 95.8 per 100,000), and the incidence of DVT is three-fold higher than PE (151.8 versus 47.9 per 100,000). PE is relatively uncommon during pregnancy compared to postpartum (10.6 versus 159.7 per 100,000).

Other conditions associated with venous thromboembolism include heparin-induced thrombocytopenia, myeloproliferative disorders (especially polycythemia rubra vera and primary thrombocythemia), intravascular coagulation and fibrinolysis/disseminated intravascular coagulation (ICF/DIC), nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, thromboangiitis obliterans (Buerger's disease), thrombotic thrombocytopenic purpura, Bechet's syndrome, systemic lupus erythematosus, inflammatory bowel disease, Wegener's granulomatosis, homocystinuria, and possibly hyperhomocysteinemia.[65,66]

THE GENETIC EPIDEMIOLOGY OF VENOUS THROMBOEMBOLISM

Recent family-based studies indicate that venous thromboembolism is highly heritable and follows a complex mode of inheritance involving environmental interaction.[67–69] Inherited reductions in plasma natural anticoagulants (e.g.,

antithrombin, protein C, or protein S) have long been recognized as uncommon but potent risk factors for venous thromboembolism.[70,71] More recent discoveries of impaired downregulation of the procoagulant system (e.g., activated protein C resistance, Factor V Leiden),[72–74] increased plasma concentrations of procoagulant factors (e.g., factors I [fibrinogen], II [prothrombin], VIII, IX, and XI)[75–79] and increased basal procoagulant activity,[80–82] impaired fibrinolysis,[83] and altered innate immunity[84] have added new paradigms to the list of inherited or acquired disorders predisposing to thrombosis (thrombophilia). These plasma hemostasis-related factors or markers of coagulation activation both correlate with increased thrombotic risk and are highly heritable.[85–89] Inherited thrombophilias interact with such clinical risk factors (e.g., environmental risk factors) as oral contraceptives,[90] pregnancy,[91] hormone therapy,[92] and surgery[93] to increase the risk of incident venous thromboembolism. Similarly, genetic interaction increases the risk of incident[94] and recurrent venous thromboembolism.[95–99] These findings support the hypothesis that an acquired or familial thrombophilia may predict the subset of exposed persons who actually develop symptomatic venous thromboembolism. Although the clinical utility of diagnostic testing for an inherited or acquired thrombophilia remains controversial, such studies hold the potential for further stratifying individual patients in to high- and low-risk for incident and recurrent venous thromboembolism, targeting prophylaxis to those who would benefit most, and, ultimately, reducing the occurrence of venous thromboembolism.

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CHAPTER

37

Fundamental Mechanisms in Venous Thrombosis

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INFLAMMATION AND VENOUS THROMBOSIS

Rationale

Venous thromboembolic disease represents an ideal opportunity for advancing our understanding of inflammation within the vascular system. A great deal of progress has been made in the interdependent fields of selectin, microparticle, phospholipid, and platelet biology in recent years. Much of this knowledge has been acquired through the utilization of models of venous thrombosis and the compilation of data from patients with deep vein thrombosis. Present therapy directed at venous thromboembolic disease (VTE) relies on anticoagulation strategies with their associated risk of severe bleeding complications. Our work is directed toward developing and testing new, targeted therapies for VTE that will be safer and more effective. These therapies will exploit new knowledge of the inflammatory mechanisms leading to venous thrombosis.

Background

Deep vein thrombosis (DVT) and its acute and chronic sequelae are a significant source of morbidity, mortality, and cost to the American public. American Heart Association statistics document two million cases of DVT each year with the incidence of DVT increasing as the population ages.[1] Pulmonary embolus (PE) accounts for 200,000 deaths each year, and the annual cost of the treatment of VTE is measured in billions of dollars.[2] We have found that VTE is noted in one percent of all medicare inpatient discharges.[3]

Chronic venous insufficiency (CVI) is a late complication of DVT suffered by nearly seven million Americans. The 20-year incidence of CVI is 28% following deep vein thrombosis, although some have suggested the incidence is higher. The symptoms include swelling, discomfort, and skin changes ranging from stasis pigmentation to frank ulceration requiring chronic wound care.[4] Chronic thromboembolic pulmonary hypertension (CTPH) has a two-year incidence of 3.8% following PE, leading to severe debilitation and high mortality.[5]

Anticoagulation is the keystone of contemporary therapy for VTE but carries a significant risk of severe bleeding. Ten percent of patients suffer minor to moderate hemorrhagic complications each year, and the annual incidence of life-threatening hemorrhage is 2%.[6,7] The risk of bleeding complications on heparin therapy is dose dependent, with a 7% increase in risk for each 10-second increase in the aPTT value.[8] Data from early studies revealed a lower incidence of bleeding complications with low molecular weight heparin versus unfractionated heparin, but recent studies have demonstrated no significant difference.[9] The risk of a major bleeding complication in the first three months of treatment with heparin initially followed by coumadin is 3%, with a significantly higher incidence in cancer patients.[10] The incidence of major bleeding complications in patients on coumadin maintained with an INR of 2.0–3.0 is half that of someone maintained with an INR of more than 3.0. Coumadin can be difficult to dose, and variability in the INR is independently associated with an increased frequency of hemorrhage.[11]

Patients managed with present optimal therapy have a 20% incidence of thrombus extension or recurrence.[12] Heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) can complicate both unfractionated and low molecular weight heparin therapy resulting in arterial and venous thrombotic complications.[13] Heparin-based therapies

also raise valid concerns regarding side effects such as the loss of bone mineral density and alopecia.[14,15]

Systemic thrombolytic therapy has not demonstrated consistent efficacy due to difficulties in patient selection and an unacceptable risk of catastrophic bleeding complications.[16,17] Catheter-directed thrombolysis in the first week following ileofemoral DVT formation has a lower incidence of bleeding complications and has demonstrated benefit in terms of venous patency and a decreased incidence of CVI.[18]

The development of new therapies for the treatment of VTE and the prevention of its sequelae will require a more thorough understanding of venous thrombosis, propagation, and resolution. The goals of any new therapy should be a reduction in hemorrhagic complications and increased efficacy.

Inflammation and Thrombosis

In the 1850s, Ludwig Rudolf Karl Virchow postulated what came to be known as *Virchow's Triad* of risk factors for DVT formation: blood stasis, vessel wall injury, and changes in the constituents of blood (hypercoagulability). A contemporary view still benefits from this framework but is informed by knowledge of genetics and molecular biology. Mammalian physiology strikes a fine balance among coagulation factors, inhibitors of coagulation, and fibrinolytic factors to optimize hemostasis while maintaining fluidity and end-organ oxygen delivery. There are many described perturbations in this balance leading to hemophilic and thrombophilic disorders. These perturbations are discussed in detail in other chapters of this text.

A significant advance from the time of Virchow occurred with the work of Stewart et al. in 1974, who suggested a link between vascular inflammation and thrombosis.[19] Stewart's original hypothesis stated that the initiating factors that promote thrombosis cause the activation of leukocytes and platelets. She proposed that this activation leads to the localization of leukocytes and platelets to the area of injury, resulting in amplification of the thrombus. Advances in molecular biology since 1974 have allowed the elucidation of the relationship between inflammatory mediators and pathways with the coagulation cascade. Inflammatory mediators upregulate procoagulant factors and downregulate natural anticoagulants while inhibiting fibrinolysis (see Table 37.1).[20] These may be systemic mediators of inflammation such as the pro-inflammatory cytokine TNFα, cytokines released locally from the area of injury such as IL-6 and IL-8, or factors localized within the growing thrombus such as thrombin. Our research has focused on strategies to treat venous thrombosis and prevent vein wall fibrosis via inhibition of selectin signaling.

TABLE 37.1 Impact of Inflammation on Coagulation (Adapted from Esrnon[20])

Elevated	Tissue factor
	Negatively charged phospholipids
	Platelet reactivity
	Fibrinogen
	Selectins
Diminished	Thrombomodulin
	Endothelial protein C receptor
	Activated protein C half life
	Protein Z
	Vascular heparins
	Fibrinolysis

SELECTIN AND MICROPARTICLE BIOLOGY

Selectin Overview

The selectins are a well-conserved family of glycoprotein, transmembrane molecules expressed on the surface of leukocytes, platelets, and endothelial cells. They play a crucial role in leukocyte and platelet rolling and adhesion to areas of vascular injury and inflammation.[21] Three selectins have been described: L-selectin, E-selectin, and P-selectin. P-selectins are stored as transmembrane proteins in preformed cytoplasmic granules mobilized by activated platelets and endothelial cells. E-selectin is inducible on vascular endothelium, and L-selectins are expressed by nearly all leukocytes.

The selectin family has a unique extracellular structure consisting of an amino terminal calcium dependent lectin domain, an epidermal growth factor-like domain, and two to nine consensus repeat sequences (CRS) that are homologous to complement binding domains. They also possess a lipophilic transmembrane domain and a short cytoplasmic tail. The variable structural length of consensus repeat sequences determines which complementary ligand carbohydrates the conserved lectin and epidermal growth factor domains it will interact with.[22] L-selectin has two consensus repeat sequences, E-selectin six consensus repeat sequences and P-selectin nine consensus repeat sequences.

Leukocyte adhesion to endothelium is controlled by the binding of vascular selectins to leukocyte expressed glycoproteins or glycolipids containing the tetrasaccharide sialyl-Lewis^x (sialic acid, galactose, fucose and N-acetylgalactosamine).[22] The ligands for P-selectin (PSGL-1) and E-selectin (not well defined) are found on leukocytes, and the ligands for L-selectin (CD34, MAdCAM-1) are found on endothelial cells. Each ligand functions by presenting O-linked saccharide chains to the calcium dependent lectin domain on the corresponding selectin. Our research has focused on modulating the P-selectin:PSGL-1 signaling axis with the therapeutic goals of preventing DVT formation,

treating established DVTs and preventing chronic venous insufficiency.

Selectin Biology

P-selectin is stored in the alpha granules of platelets and in the Weibel-Palade bodies of endothelial cells (EC).[23] Exposure to an activating stimulus such as thrombin results in rapid translocation of P-selectin to the cell surface, avoiding the need for transcription or translation.[24] E-selectin is upregulated after the initiation of thrombosis in a transcription-dependent fashion. P-selectin can be secreted into the circulation as a component of EC and platelet-derived microparticles (MP) or, in small quantities, as a free, alternatively spliced version lacking a transmembrane domain.[25] These two forms of soluble P-selectin are elevated in humans in association with atherosclerosis and thrombosis and are predictive of future adverse cardiovascular events, including myocardial infarction and stroke.[26–28] Soluble P-selectin levels are also elevated at times of overwhelming systemic thrombosis and consumption, such as disseminated intravascular coagulation and heparin-induced thrombocytopenia.[29]

P-selectin plays a critical role in the initial adhesion and rolling of platelets and leukocytes to areas of injury and inflammation via the P-selectin receptor, P-selectin glycoprotein ligand-1 (PSGL-1). P-selectin also plays a prominent role in hemostasis and thrombosis through PSGL-1 signaling in leukocytes and platelets and GPIbα in platelets. P-selectin deficient mice demonstrate a hemophilic phenotype with marked bleeding tendencies.[30] Mice with a deletion of the transmembrane domain of P-selectin have elevated levels of circulating P-selectin resulting in thrombophilia. P-selectin based therapy has been demonstrated to correct a mouse model of hemophilia.[31]

In animal models of DVT, we, and others, have demonstrated that P-selectin expression regulates fibrin deposition and thrombus size.[32,33] We have also demonstrated that P-selectin and E-selectin deletions are associated with decreased thrombosis and that the thrombi have decreased fibrin content.[34] In a primate model of stasis-induced DVT, P-selectin blocking antibodies or antibodies blocking the P-selectin receptor, PSGL-1, inhibit thrombosis and promote recanalization.[35,36] In animal models we have found that P-selectin blockade with monoclonal antibodies has been found to be as effective as low molecular weight heparin in promoting thrombus resolution and preventing vein wall thrombosis, all without the risk of hemorrhagic complications.[37]

We have also demonstrated that P-selectin inhibition is an effective treatment for established primate and rodent iliofemoral DVT through augmentation of fibrinolytic activity.[38] The findings of an improvement in spontaneous thrombolysis in animals in which P-selectin is inhibited by rPSGL-Ig are similar to results found in primate, porcine, and rat models of arterial and venous thrombosis using P-selectin inhibition.[36,39–41] A reduction in the fibrin content of thrombi formed in the presence of P-selectin inhibition is likely contributory, as leukocyte-platelet interactions leading to fibrin deposition are P-selectin dependent.[33]

Microparticles

Microparticles (MP) are small (less than 1 micrometer, about the size of a bacterium) phospholipid vesicles that are shed from a variety of cell types including platelets, leukocytes, and endothelial cells.[42–44] Microparticles are a normal constituent of blood and can be isolated from plasma by ultracentrifugation. Microparticles lack DNA and RNA but are protein rich. All circulating blood cells, platelets, and endothelial cells are capable of releasing MP in a calcium-dependent fashion. The protein expression profile of MP depends on the mother cell of origin and the conditions influencing their production. The protein and phospholipid content of MP determines the biologic activity of MP with regard to hemostasis and other physiologic processes. Subpopulations of MP rich in tissue factor (TF) and phosphatidylserine, two critical components of the coagulation cascade, have been identified.[45,46] Several circulating markers of inflammation once thought to be soluble actually are carried by MP.[47]

Lipid rafts are sphingolipid ordered, cholesterol-rich microdomains floating within the more fluid cell surface bilayer (the "fluid mosaic").[48] These rafts allow for the concentration of receptor clusters, G-proteins, adaptor proteins, and downstream kinases to facilitate signal transduction through the concentration of the proximal machinery of cell signaling pathways.[49] Apoptotic blebs and microparticles are derived from raft-rich regions of the plasma membrane, resulting in high concentrations of cholesterol, negatively charged phospholipids, and protein complexes, as compared with the cell of origin.

Microparticles are rich in the external leaflet aminophospholipids phosphatidylethanolamine and phosphatidylserine providing a critical, negatively charged substrate for coagulation. Under quiescent conditions, membrane asymmetry is maintained by the active transport of nonthrombotic, choline phospholipids to the outer leaflet in exchange for aminophospholipids by the enzymes flippase and floppase. Cellular activation results in the induction of scramblase activity and the inhibition of flippase. This results in a loss of asymmetry and induction of a procoagulant phenotype.[50] Inability to mobilize aminophospholipids to the outer membrane leaflet due to defective phospholipid translocation results in a bleeding tendency manifested as Scott syndrome.[51]

Rafts and raft-derived MP can concentrate tissue factor (TF) in cavaolae where it is stored with tissue factor pathway

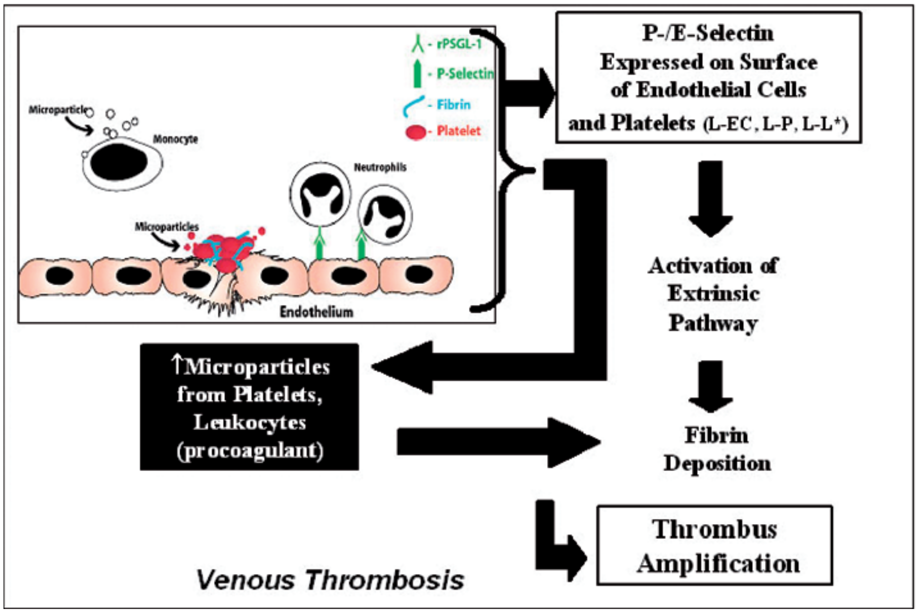

FIGURE 37.1 The role of microparticles in thrombus amplification (Adapted from Myers et al[61]).

inhibitor (TFPI).[52] Fusion of MP with activated platelets results in decryption of TF and the initiation of thrombosis.[53] Monocytes concentrate TF and PSGL-1 in rafts. Monocyte-derived MP deliver TF to areas of injury and inflammation by binding to P-selectin mobilized to the surface of activated platelets and EC, resulting in the generation of fibrin (see Figure 37.1).[45] Through the depletion of cholesterol in the raft regions of platelets and leukocytes, statin drugs may decrease the risk of thrombosis through raft architectural disruption. Cholesterol-depleted platelets and leukocytes are less adherent and may release less thrombotic MP.[54]

The P-selectin receptor, PSGL-1, is expressed on leukocytes and platelets as well as on their derived microparticles. MP coexpressing TF and leukocyte markers have been shown to accumulate in growing thrombi in a PSGL-1: P-selectin dependent fashion.[55,56] P-selectin:PSGL-1 interactions also stimulate the production of thrombogenic MP from leukocytes, particularly monocytes.[31,57] These prothrombotic MP express TF and possess a phosphatidylserine rich anionic surface capable of assembling prothrombinase, tenase, and factor V/Va.[58] Hrachinova et al. treated mice with hemophilia A with P-sel-Ig to generate prothrombotic MP. This normalized tail bleeding times and systemic coagulation times through augmentation of the extrinsic coagulation pathway.[31] This strategy may result in new therapies for hemophilia A patients with alloantibodies. Human pericardial MP expressing TF have been demonstrated to increase thrombosis in a rat venous stasis model.[59] Venous stasis and ischemia results in the upregulation of vascular P-selectin, which localizes prothrombotic MP to the area of stasis and promotes DVT formation (see Figure 37.1).[60–62]

In some vascular models of injury, P-selectin dependent TF accumulation and fibrin deposition begins within the first 20 seconds of injury, before leukocyte rolling occurs, suggesting that a major function of selectins in venous thrombogenesis is independent of leukocyte rolling and extravasation. P-selectin:PSGL-1 interactions are critical for the localization of prothrombotic MP to areas of injury and inflammation.[63,64] The relative importance of MP-born TF in thrombosis appears to vary according to the nature and scope of the injury. MP appear to play a critical role in stasis-induced thrombosis and small vascular injuries. Chou et al. demonstrated that leukocyte-derived TF contributed significantly to thrombus formation after laser injury of the microvessels in the cremaster muscle, a small injury model. Day et al. demonstrated that leukocyte-derived TF did not contribute significantly to thrombosis following treatment of the carotid artery with ferric chloride, a dramatic, somewhat artificial and large-scale injury. It is likely that MP-bearing tissue factor contribute to the initial thrombus formation and amplification that occurs in the minutes following small scale vascular injuries (see Figure 37.2).[62]

Microparticles are not only prothrombotic but also appear to inhibit fibrinolysis. Platelet activator inhibitor-1 (PAI-1) is stored in the α-granules of quiescent platelets.[65] PAI-1 is a potent inhibitor of tissue plasminogen activator (tPA) and urokinase-type plasminogen activators, which are largely responsible for the initiation of fibrinloysis.[66] Upon activation, MP shed from platelets express PAI-1, and these MP are localized to the growing thrombus via P-selectin-PSGL-1 interactions. In this manner, platelet microparticles are not

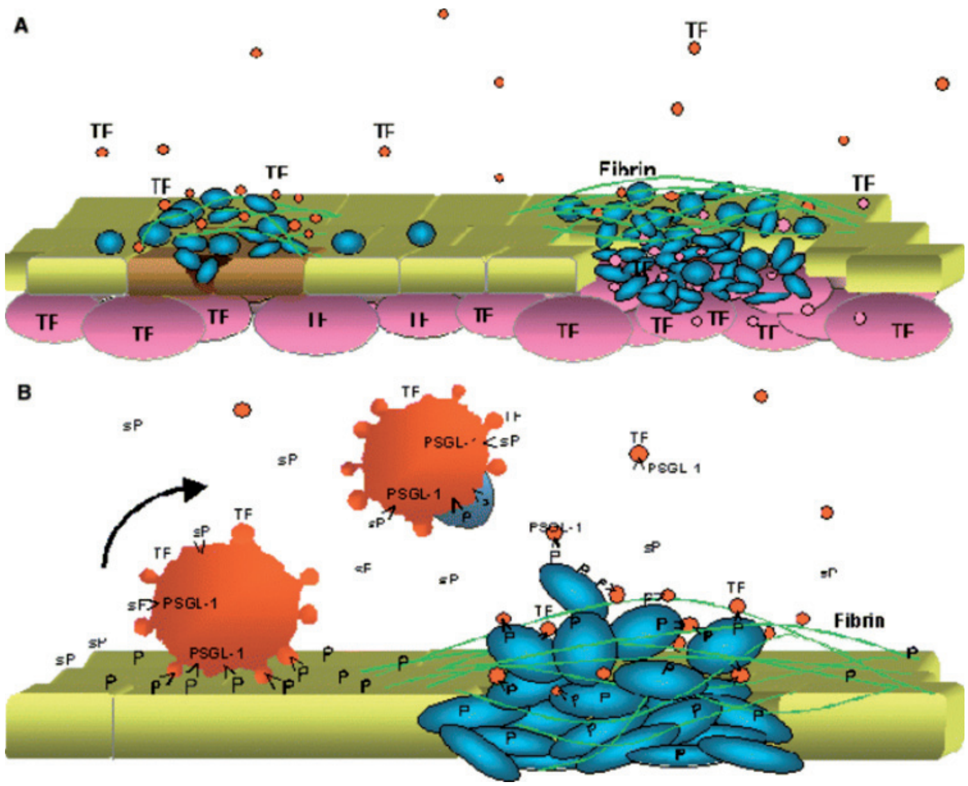

FIGURE 37.2 Proposed role of tissue factor in vessel wall injury (Adapted from Polgar et al[62]).

only prothrombotic but also inhibit fibrinolysis, delaying thrombus resolution.[67]

Translating P-selectin and Microparticle Research

Traditional anticoagulation is contraindicated in many patients and results in significant hemorrhagic complications. Patients on optimal therapy have a 20% incidence of thrombus recurrence or extension. The new, inflammatory perspective on VTE has opened up a line of attack along the axis of selectin biology. Presently, we are conducting rodent and primate research on the prophylactic and therapeutic use of compounds that inhibit P-selectin or its receptor, PSGL-1, and that can be delivered by multiple routes for use in VTE.

D-dimers are a plasmin breakdown product of insoluble, cross-linked fibrin. Although D-dimers are elevated in patients with VTE, this finding has a specificity of only 50 to 70%. In current practice D-dimer is useful only when negative in association with patients with low clinical assessment scores.[68]

The abundance of evidence supporting an important role for P-selectin and MP in thrombosis led us to hypothesize that they may be reliable clinical indicators of an ongoing, thrombotic event. We have found that a panel of blood tests including D-dimer, P-selectin, and MP levels is more sensitive and specific for the detection of DVT than D-dimer alone, though still less sensitive than duplex ultrasound (US). This panel would be most useful in locations or at times when duplex US is unavailable. As our knowledge of microparticle subtypes and protein expression improves, it is likely that even more definitive tests for the detection of thrombotic events and assessment of overall cardiovascular risk will become available.

THROMBOSIS RESOLUTION AND VEIN WALL FIBROSIS

The resolution of a deep vein thrombus parallels the traditional model of wound healing with a predictable orchestration of leukocyte infiltration, the elaboration of profibrotic growth factors and collagen deposition. This process is required for thrombus resolution and neovascularization but also results in vein wall fibrosis, valvular incompetency, and subsequent CVI. There is indirect clinical evidence that the length of time the thrombus is in contact with the vein wall is proportional to the magnitude of the fibrotic response. Early, aggressive anti-coagulation and catheter-directed thrombolysis result in earlier thrombus resolution and a reduction in the risk of CVI.

Neutrophils are the first cell type to infiltrate the thrombus and play an essential role in thrombus resolution.[69] Neutropenia is associated with larger thrombi in a rat model of stasis DVT and treatment with IL-8, a neutrophil stimulatory and chemotactic cytokine, accelerates thrombus resolution.[70,71] Mice lacking the receptor for the IL-8 analogs KC and MIP-2 have larger and less organized thrombi due to the lack of neutrophil infiltration.[72]

Monocyte and monocyte-derived macrophage infiltration follows the neutrophil phase. Monocyte infiltration peaks on day 8 after formation of a stasis-induced DVT in animal models and is dependent on the elaboration of monocyte chemoattractant protein-1 (MCP-1) from the site of injury. Exogenous introduction of MCP-1 into a newly formed thrombus accelerates recanalization and resolution.[73] Experimental over-expression of MCP-1 accelerates thrombus resolution, and we have found that strategies that inhibit monocyte infiltration also inhibit thrombus resolution.

As venous thrombi resolve they demonstrate increased urokinase-type plasminogen activator (u-PA) and tissue plasminogen activator (t-PA) activity.[74] The in vivo expression of u-PA and t-PA activity is monocyte dependent.[75] A series of experiments utilizing bone marrow transplantation strategies in knock-out mice have revealed that monocyte expressed u-PA plays a more critical role in thrombus resolution as compared to t-PA.[76] Monocytes further degrade fibrin via receptor-mediated lysosomal activity.[77] Modulation of monocyte infiltration and the fibrinolytic pathway are potential targets for the treatment of VTE and prevention of CVI.

The actions of infiltrating leukocytes are critical for thrombus resolution but also result in the elaboration of profibrotic cytokines including TGF-β, RANTES, and MCP-1.[78] The kinetics of leukocyte invasion into the thrombus are duplicated in the vein wall with an initial wave of neutrophil invasion followed by monocyte infiltration. Elastinolysis occurs early, resulting in diminished vein wall compliance. Collagen I and collagen III deposition follow, further stiffening the vein wall.

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CHAPTER

38

Congenital and Acquired Hypercoagulable Syndromes

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INTRODUCTION

A fine balance exists between anticoagulant, procoagulant, and fibrinolytic factors. Intravascular thrombosis represents a shift in this balance, and may occur as the result of many factors in conjunction with a congenital or acquired abnormality in coagulation. An understanding of the differing hypercoagulable syndromes is important to appreciate the complexity of hemostasis and the factors that may offset normal clotting and anticoagulant mechanisms (see Figure 38.1). In addition, methods of prophylaxis and treatment of venous thromboembolism are increasingly being stratified based, in part, on the presence or absence of a thrombophilic state. The presence of a hypercoagulable state does not imply that the patient will have thrombosis of a vessel. It does suggest that the individual is at a higher risk for thrombosis especially when the other factors of Virchow's triad (endothelial injury and stasis) are involved.[1]

CONGENITAL VS. ACQUIRED HYPERCOAGULABLE STATES

Some congenital hypercoagulable states place the individual at higher risk for thrombosis than others. Most genetic abnormalities in existence have clinically imperceptible consequences.[2,3] Additionally, some individuals have multiple genetic abnormalities, increasing their risk of thrombosis.[4] The common congenital hypercoagulable disorders are listed in Table 38.1.

Many causes exist for acquired hypercoagulable states and some congenital hypercoagulable states may exist as acquired states as well. For instance, Protein C and S deficiencies may occur secondary to decreased protein production from liver failure, sepsis, and/or malnutrition and increased protein loss secondary to nephrotic syndrome and inflammatory states.[5] In addition, hyperhomocysteinemia may occur because of enzymatic defects or because of deficiencies in Vitamins B_6 and B_{12} and folate. The acquired hypercoagulable disorders are listed in Table 38.2.

THE CONGENITAL HYPERCOAGULABLE DISORDERS

Antithrombin Deficiency

Antithrombin is a serine protease inhibitor of thrombin and also inhibits factors IXa, Xa, XIa, and XIIa. Thrombin is irreversibly bound by antithrombin and prevents thrombin's action on fibrinogen, on factors V, VIII, and XIII, and on platelets.[6] This anticoagulant is synthesized in the liver and endothelial cells, and has a half-life of 2.8 days.[7] Antithrombin deficiency has a prevalence of 1 : 5000 with more than 100 genetic mutations and an autosomal dominant inheritance pattern.[8] Homozygotes typically die *in utero* whereas heterozygotes typically have an antithrombin level that is 40 to 70% of normal.

Antithrombin deficiency is associated with lower extremity venous thrombosis as well as mesenteric venous thrombosis, and there are two clinical types. Individuals with Type I deficiency have a reduced number and function of antithrombin, and individuals with Type II have normal production but a reduction in function. Additionally, the heparin binding site of the antithrombin may be mutated.[9] The risk of thrombosis increases as the functional antithrombin activity decreases to less than 80% of normal levels. The highest risk for thrombosis occurs when the activity is less than 60% of normal.[1]

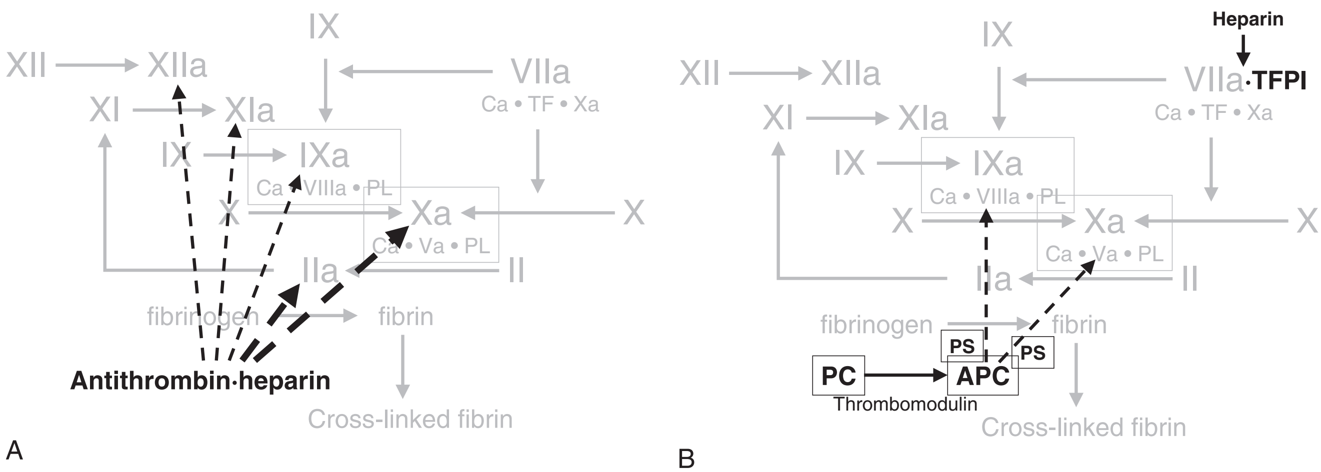

FIGURE 38.1 The coagulation cascade (light grey) and the sites of action for the natural anticoagulants (black). PC = protein C, APC = activated protein C. Protein S (PS) is a cofactor for the inhibition of factors V and VIII. TFPI (tissue factor pathway inhibitor) levels increase several fold in response to heparin. TFPI binds to factor VIIa, inhibiting the conversion of factor X to Xa, and factor IX to IXa.

TABLE 38.1 The Most Common Congenital Hypercoagulable Disorders

Congenital hypercoagulable disorders
Antithrombin Deficiency
Protein C Deficiency
Protein S Deficiency
Factor V Leiden
Prothrombin G20210A Polymorphism
Hyperhomocysteinemia
Dysfibrinogenemia and Abnormal Fibrinogens

TABLE 38.2 Acquired Hypercoagulable Disorders

Acquired hypercoagulable disorders	
Heparin Induced Thrombocytopenia/ Heparin Induced Thrombocytopenia and Thrombosis Syndrome	Hyperfibrinogenemia
Lupus Anticoagulant/Antiphospholipid Antibody Syndrome	Nephrotic Syndrome
Smoking	Renal Failure
Warfarin	Vasculitis
Pregnancy	Malignancy
Oral Contraceptive Pills/Hormone Replacement Therapy	Thrombocythemia
Mechanical Injury/Trauma/Surgery	Homocysteinemia
Diabetes Mellitus	Sepsis
Hyperlipidemia	Obesity
Polycythemia vera	Immobility

The most common presentation in those with antithrombin deficiency is deep venous thrombosis with or without pulmonary embolism.[10] The frequency of thromboembolism is unusual before the late teenage years and plateaus around the age of 40.[11] Thromboembolism may occur spontaneously but is often precipitated by other factors such as pregnancy, oral contraceptive use, estrogen replacement, trauma, surgery, or infection.[12]

Antithrombin deficiency should be suspected in a patient with spontaneous thrombosis, in a patient who cannot be anticoagulated adequately on heparin or in a patient who develops thrombosis while on heparin. To detect this deficiency, antithrombin levels should be measured when the patient has not been exposed to heparin.[13,14]

Protein C and Protein S Deficiency

Protein C is a vitamin K dependent anticoagulant protein that, once activated by thrombin, will inactivate factors Va and VIIIa, thereby inhibiting the generation of thrombin.[4] Additionally, activated protein C stimulates the release of t-PA. It is produced in the liver and is the dominant endogenous anticoagulant with an eight-hour half-life. Protein C deficiency has a prevalence of 1 in 200–300 with more than 150 mutations and an autosomal dominant inheritance.[4,7] Similar to antithrombin deficiency, protein C deficiency has two types: Type I, which is associated with decreased production and function and Type II, which is associated with a low functional level.[8] Type I deficiency predominates.

Protein S is also a vitamin K dependent anticoagulant protein that is a cofactor to activated protein C. The actions of protein S are regulated by complement C4b binding protein and only the free form of protein S serves as an activated protein C cofactor.[15] Additionally, protein S appears to have independent anticoagulant function by directly inhibiting procoagulant enzyme complexes.[7,16] The prevalence of protein S deficiency is about 1 : 500 with an autosomal dominant inheritance. Three types of protein S deficiencies exist and include Type I, which is associated with low levels of free and total protein S antigen and

decreased activated protein C activity; Type II, which has normal levels of protein S antigen but low levels of activated protein C cofactor activity; and Type III, which has normal to low levels of total protein S, low free protein S, and an increased proportion of protein S bound to complement C4b.[8] In addition, many patients with protein S deficiency also have resistance to activated protein C, which may be the reason for the thrombosis.[1]

Clinically, protein C and S deficiencies are essentially identical. With homozygous protein C and S deficiencies, infants typically will succumb to purpura fulminans, a state of unrestricted clotting and fibrinolysis. In heterozygotes, venous thromboses may occur at an early age especially in the lower extremity.[17] Thrombosis may also occur in mesenteric, renal, and cerebral veins. Protein C and S deficiencies usually become clinically evident when the levels of these proteins are less than 50% of normal.

Plasma protein C and S concentrations may be obtained to diagnose deficiencies of these proteins. Antigen and activity levels of protein C are measured, whereas for protein S, only antigen levels are measured. These measurements should be made prior to starting anticoagulation therapy with either heparin or warfarin.[8,13,18]

Factor V Leiden Mutation and Activated Protein C Resistance

Factor V is a glycoprotein synthesized in the liver. With Factor V Leiden, a point mutation occurs when arginine is substituted by glutamine at position 506. This point mutation causes the activated Factor V to be resistant to inactivation by activated protein C thus causing a procoagulant state. The mutation appears almost exclusively in the Caucasian population and inheritance is autosomal dominant. The relative risk of a thromboembolic event in a heterozygous carrier is increased five- to seven-fold over the general population and increased up to 80-fold in a homozygous carrier.[4] The risk of thrombosis also increases with combined genetic defects and/or additional acquired risk factors and will exceed the sum of the separate risks.[15]

Clinically, patients may present with deep venous thrombosis in the lower extremities, or less commonly in the portal vein, cerebral vein, or superficial venous system. Laboratory testing for the diagnosis of activated protein C (APC) resistance and Factor V Leiden may be performed using functional clotting based assays or by genetic testing. Factor V Leiden is the most common cause for APC resistance. Other less common causes include Factor V Cambridge, HR2 haplotype, Factor V Hong Kong, and Factor V Liverpool. The functional clotting-based assays include a modified aPTT, which dilutes the patient's plasma in factor V deficient plasma or incorporates dilute Russell's viper venom in the assay. The presence of APC resistance is then determined by measuring the aPTT in the presence and absence of activated protein C. This modified test may be used in the presence of heparin, warfarin, and lupus anticoagulant. The genetic test relies on DNA amplification using PCR and is the most reliable test.[18]

Prothrombin G20210 Polymorphism

Prothrombin (Factor II) is a zymogen synthesized in the liver and dependent on vitamin K. When prothrombin is activated, it forms thrombin (Factor IIa). A single mutation where adenine is substituted for guanine occurs at the 20210 position. The mechanism for increased thrombotic risk is not well understood, but individuals with this genetic variant have supranormal levels of prothrombin. The mutation is inherited as an autosomal dominant trait and is associated with both arterial and venous thrombosis. Like Factor V Leiden, this mutation occurs almost exclusively in the Caucasian population. Individuals with the prothrombin gene variant are typically heterozygous.[7] Heterozygosity confers a two-fold increase in the risk of thrombosis, and homozygosity confers approximately a 10-fold increase in the risk of thrombosis.[13]

Clinically, patients may present with deep venous thrombosis of the lower extremity, cerebral venous thrombosis, as well as arterial thrombosis. The risk of thrombosis increases in the presence of other genetic coagulation defects and with acquired risk factors.[1,7] Detection of the prothrombin G20210 polymorphism is by genetic analysis alone as no correlation exists between functional prothrombin levels and those individuals with the genetic mutation.[13]

Hyperhomocysteinemia

Homocysteine is an amino acid formed during the metabolism of methionine and may be elevated secondary to inherited defects in two enzymes that are part of the conversion of homocysteine to cysteine. The two enzymes involved are N^5,N^{10}–methylene tetrahydrofolate reductase (MTHFR) or cystathionine beta-synthase. Hyperhomocysteinemia has been shown to increase the risk of atherosclerosis, atherothrombosis, and venous thrombosis.

Elevated plasma homocysteine levels cause various dysfunctions of endothelial cells leading to a prothrombotic state. With the oxidation of homocysteine, superoxide radicals are formed, which cause endothelial damage, smooth muscle proliferation, and activation of platelets and leukocytes. Additionally, hyperhomocysteinemia augments factor V and VII activity and decreases the activation of protein C, indirectly stimulates platelet aggregation, decreases the production of endothelium-derived nitric oxide, and interferes with the binding of t-PA.[1,19]

In patients with unexplained venous thromboembolism, homocysteine levels should be measured. Levels may be measured by obtaining a fasting plasma homocysteine or

after giving a standardized methionine-loading test. In patients who have been given the loading dose of methionine, hyperhomocysteinemia is present if the level of homocysteine is two standard deviations above the mean.

In patients with hyperhomocysteinemia, folate, B_6 and/or B_{12} can be given with normalization of homocysteine levels after several weeks of therapy. Whether or not this treatment has any affect on the prothombotic effects of hyperhomocysteinemia remains to be proven.[19]

ACQUIRED HYPERCOAGULABLE DISORDERS

There exist far more known causes of acquired hypercoagulable disorders than inherited disorders. Additionally, several of the congenital hypercoagulable states may be seen as acquired states due to a change in the production or consumption of various factors. Many of the common causes of acquired hypercoagulable disorders will be discussed.

Heparin-induced Thrombocytopenia (HIT) and Heparin-induced Thrombocytopenia and Thrombosis Syndrome (HITTS)

Approximately 2 to 3% of patients who undergo heparin therapy will develop HIT or HITTS. Patients with HIT will have thrombocytopenia (characterized by a platelet count less than 100,000/mm^3 or a decrease in the baseline count by more than 30%), will be resistant to anticoagulation with heparin, and may develop arterial or venous thromboses.

Two types of HIT exist. The first type is not associated with an immune mediated response and typically is seen in the first few days after initiation of heparin therapy. Typically, platelet levels do not fall below 100,000/mm^3. Type II is immune-mediated with patients producing IgG antibodies against complexes of heparin and platelet factor 4. Antibody formation usually occurs between the fifth and tenth day after the first heparin exposure. The formation of these immune complexes creates a hypercoagulable state by activating platelets and the endothelium.[8,20]

Antibodies may develop against any form of heparin and the formation of antibodies is independent of the age or sex of the patient, the route of administration of heparin, or the amount of heparin administered. Clinically, a patient will have a declining platelet count, may have an increasing resistance to anticoagulation therapy with heparin, and may develop a new thrombosis. Laboratory testing may be performed, which includes testing for antibodies to heparin.[1] Functional assays to detect platelet aggregation or activation in the presence of heparin-associated antibodies are well established. Enzyme-linked immunosorbent assays (ELISA) are readily available, but there is up to 40% discordance in the results of these antigenic assays, when compared with the functional platelet aggregation tests. The ELISA may detect IgM and IgA varieties, whereas platelet aggregation assays detect only the IgG antibodies.

The treatment of HIT includes the prompt discontinuation of heparin or low-molecular-weight heparin, and the administration of alternative anticoagulants such as recombinant hirudin or argatroban (both direct thrombin inhibitors). Danaparoid (a low-molecular-weight heparinoid) has been used in the past as an alternative anticoagulant in patients with HIT. However, danaparoid production was discontinued in 2002 due to a shortage in the drug substance. Fondaparinux (a pentasaccharide that inactivates factor Xa via an antithrombin-dependent mechanism) has had recent success as another alternative anticoagulant. As with hirudin and argatroban, there are no reliable agents that can reverse the anticoagulant effect of fondaparinux. Hirudin and fondaparinux are metabolized primarily via renal excretion, whereas argatroban is metabolized primarily by the liver.

Patients with heparin-induced thrombocytopenia are at high risk for the development of subsequent thromboses, and the discontinuation of heparin alone is usually not sufficient. Warfarin may be used for prolonged anticoagulation in patients with acute thromboses, but its initiation should be delayed until the platelet count has substantially recovered. In addition, warfarin therapy should overlap with the administration of a direct thrombin inhibitor until the platelet count normalizes.

Lupus Anticoagulant/Antiphospholipid Antibody Syndrome

The term antiphospholipid syndrome was developed to describe the clinical manifestations of a hypercoagulable state associated with antiphospholipid antibodies. The most commonly identified antiphospholipid antibodies are lupus anticoagulant, anti-cardiolipin antibody, and anti-β_2-glycoprotein I antibodies.[21]

This syndrome is divided into primary and secondary syndromes. The primary syndrome occurs in patients without associated autoimmune disorders and the secondary syndromes occur in patients with systemic lupus erythematosus and/or other autoimmune disorders. The procoagulant effects of the antiphospholipid antibodies leading to thrombosis include inhibition of the activated protein C pathway, inhibition of antithrombin activity, inhibition of anticoagulant activity of β_2-glycoprotein I, inhibition of fibrinolysis, potentiation of platelet activation, and enhanced platelet activation, among others.[8,21]

Antiphospholipid antibodies are found in 1 to 5% of the population and their prevalence increases with age. Among patients with SLE, the prevalence of antiphospholipid antibodies is much higher, with 12 to 30% having anticardiolipin antibodies and 15 to 34% having lupus anticoagulant

TABLE 38.3 Criteria for the Classification of the Antiphospholipid Syndrome[22]

International consensus statement on preliminary criteria for the classification of the antiphospholipid syndrome
Clinical Criteria:
Vascular thrombosis: 1 or more clinical episodes of arterial, venous, or small vessel thrombosis, occurring within any tissue or organ.
Complications of Pregnancy:
1 or more unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation; or
1 or more premature births of morphologically normal neonates at or before the 34th week of gestation; or
3 or more unexplained consecutive spontaneous abortions before the 10th week of gestation.
Laboratory Criteria:
Anticardiolipin antibodies
Anticardiolipin IgG or IgM antibodies present at moderate or high levels in the blood on 2 or more occasions at least 6 weeks apart.
Lupus anticoagulant antibodies
Lupus anticoagulant antibodies detected in the blood on two or more occasions at least six weeks apart.

antibodies. In patients with SLE and an antiphospholipid antibody, 50 to 70% may develop the antiphospholipid syndrome.[1] In order for the diagnosis of antiphospholipid syndrome to be made, the patient must meet the criteria of the International Consensus Statement. A definitive diagnosis may be made if the patient has at least one of the clinical criteria and one of the laboratory criteria. The Consensus Statement is defined in Table 38.3.

Clinically, the most common manifestation of the antiphospholipid syndrome is deep venous thrombosis of the legs. Arterial thrombosis also may be seen but less often than venous thrombosis. Laboratory tests to detect the antiphospholipid antibodies include the activated partial thromboplastin time (aPTT), performed with and without exogenous normal plasma to detect the presence of an inhibitor. Other tests include the kaolin clotting time, and dilute Russell's viper venom time (dRVVT). ELISA tests are performed to detect anticardiolipin antibodies and anti-β_2-glycoprotein I antibodies.[21]

Aspirin and hydroxychloroquine have been used in subsets of patients with the antiphospholipid syndrome for prophylaxis against thrombotic events. The treatment of established venous thromboembolism in these patients consists of acute heparinization and longer-term (possibly life long) vitamin K antagonists. The optimal intensity of warfarin anticoagulation (INR 2.0–2.9 versus 3.0–3.9) has not been determined.[21]

Warfarin-induced Skin Necrosis

This disorder is the most severe nonhemorrhagic complication of oral anticoagulation. Although rare, it seems to show a predilection for perimenopausal obese women who are being anticoagulated. Venules and capillaries within the subcutaneous fat and overlying skin thrombose, leading to necrosis. This typically is seen in the subcutaneous fat of the breasts, thighs, buttocks, and legs. Clinically, the patient may initially have paresthesias, which are then followed by painful, erythematous lesions. When hemorrhagic bullae are present, this is indicative of full thickness skin necrosis.

The pathogenesis for this process is the depletion of protein C prior to the other vitamin K-dependent coagulation factors. As the half-life of protein C is only eight hours, its rapid depletion causes a transient hypercoagulable state until the rest of the vitamin K-dependent factors also are reduced to levels that produce anticoagulation.

The primary treatment is prevention with heparin or low-molecular-weight heparin anticoagulation for the first 48 to 72 hours of anticoagulation with warfarin. If skin necrosis develops, warfarin needs to be discontinued and anticoagulation may continue with heparin or a direct thrombin inhibitor.[8]

Surgery/Trauma

The risk of thrombosis is dependent on the type of surgery and the presence of additional risk factors. This risk may persist for up to several months after surgery. Patients who are at particularly high risk include those who undergo hip fracture surgery, hip or knee arthroplasty, neurosurgical procedures, and patients with major trauma. Injury to tissues and vessels during the procedure may enhance thrombogenesis.[8,23] Operative dissection, thermal injuries, and soft tissue trauma activate the coagulation cascade by inducing tissue factor release, thereby increasing the thrombogenic risk.

With a major traumatic injury, risk for venous thrombosis is highest in patients with spinal injuries, pelvic fractures, and lower extremity fractures. The risk of thrombosis also increases with greater injury severity. In part, this may be due to the accompanying systemic inflammatory response (another prothrombotic state, covered later).

Pregnancy

During pregnancy, there is an associated hypercoagulable state due to the increase in factors I, VII, VIII, IX, X, XI, and XII. Additionally, platelet counts increase and concentrations of protein S and antithrombin decrease. The fibrinolytic system also may be inhibited secondary to the increased production of plasminogen-activated inhibitors 1 and 2 by the placenta. Compounding this risk is the degree of stasis that occurs as a result of compression of the lower extremity veins by the gravid uterus. In the postpartum period, the risk for thrombosis is up to five times greater than during pregnancy. Approximately two months after delivery, the coagulation and fibrinolytic systems will return to normal.[1]

The risk of thrombosis is increased further in pregnant women who have a genetic risk for thrombosis. Depending on the inherited thrombophilia, a woman with a thrombophilia who becomes pregnant may have a risk of venous thrombosis up to eight times higher than those without a thrombophilia.[4] In addition, women with a genetic risk for thrombosis are also at an increased risk for fetal loss and pre-eclampsia. Many women with a history of thrombophilia or thromboembolism are treated with heparin, low-molecular-weight heparin, and/or aspirin while pregnant.[24]

Oral Contraceptive-related Thrombosis

Oral contraceptives are one of the most frequently used drugs by women. The use of oral contraceptives initially was associated with a three-fold increased risk of venous thrombosis. With the decrease in the amount of estrogen placed in the pill, a subsequent decrease in the incidence of venous thrombosis was seen. With lower levels of estrogen, the risk of thrombosis is 1.5 to 2 times that over control patients. Additionally, newer oral contraceptives using newer progesterones have shown an increased risk of thromboembolism.[25]

The risk for venous thrombosis is highest during the first year of use of the oral contraceptive and the risk is not cumulative with prolonged use. Once the pill is discontinued, the risk returns to baseline for that patient.[25,26]

Oral contraceptives influence the plasma levels of nearly every protein involved in coagulation. Factors VII, VIII, IX, X, and XI increase, and the natural anticoagulants antithrombin and protein S decrease. However, oral contraceptive administration is associated with elevated protein C, α_1-antitrypsin, and fibrinolytic proteins, producing an antithrombotic effect. Additionally, the pill has been associated with an acquired activated protein C resistance occurring within three days of initiation of the pill and reversing with discontinuation. This resistance has been shown to have a more pronounced increase in those women using third-generation oral contraceptives. The combination of activated protein C resistance, increased prothrombin levels, and decreased protein S levels produces a net prothrombotic affect and confers the prothrombotic risk of oral contraceptives.[27,28]

In women with inherited thrombophilias who also take oral contraceptives, the risk for thrombosis increases 30- to 50-fold. For example, women who take oral contraceptives and are heterozygous for the Factor V Leiden mutation have been shown to have an increased risk of venous thrombosis by a factor of approximately 35. This increased relative risk for venous thrombosis is in the same order of magnitude as patients who are homozygous for the Factor V Leiden mutation (almost 50-fold increased risk). The women who have other inherited thrombophilias also appear to have a remarkably increased risk.[4,25]

Hormone Replacement Therapy–related Thrombosis

Historically, hormone replacement therapy (HRT) has been used to reduce the progression of osteoporosis, relieve the symptoms of menopause, and reduce the cardiovascular risk profile. Several studies including the Heart Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) have shown an increased risk of venous thromboembolism with the use of HRT. A two- to four-fold increased risk, compared to nonusers, has been shown.[26,29]

Similar to oral contraceptives, the risk of venous thromboembolism is highest during the first year of HRT. Once HRT is discontinued, the risk of thrombosis returns to baseline. Additionally, increasing age has been associated with an increased risk of venous thrombosis. Several studies also have shown an increased risk in patients using HRT who had lower extremity fractures, recent surgery, previous venous thromboembolism, cancer, and obesity.[29] Also similar to oral contraceptive pills, patients on HRT with thrombophilias have a significantly increased risk of venous thromboembolism.[4] The coagulation factor changes, which occurs as a result of hormone replacement therapy, and is similar to those changes that occur with oral contraceptive pills, but to a lesser degree.

Systemic Inflammatory Response (SIR) and Sepsis

With the systemic inflammatory response, cytokines and other inflammatory mediators are released causing a prothrombotic state. Specifically, tumor necrosis factor α and interleukin-1α are increased. These factors activate the coagulation cascade, cause an increase in tissue factor expression, and decrease levels of protein C and S. Fibrinogen synthesis also will increase as part of the inflammatory response. Additionally, the inflammatory response is enhanced by thrombin, which augments leukocyte adhesion and activates platelets. Platelet activation in turn, further promotes tissue factor expression and increases cytokine release. All these factors contribute to the hypercoagulable state seen with SIRS and sepsis and predispose the patient to thrombosis.[30]

Malignancy

Venous thromboembolism (VTE) is a common complication of cancer. In 10% of patients who present with an idiopathic VTE, malignancy will be discovered. The majority of thrombotic episodes occur spontaneously, although patients with cancer often have other concurrent risk factors (inherited thrombophilias, immobilization, major surgical proce-

dures, chemotherapy, and central venous catheters) that place them at high risk for venous thromboembolism.

Tissue factor and cancer procoagulant are produced by tumor cells. The cancer procoagulant directly activates factor X independently of factor VII. Additionally, tumor cells produce proteins that may regulate the fibrinolytic system. These proteins impair fibrinolytic activity leading to a prothrombotic state.[31] Tumor cells also produce various cytokines and affect the coagulation cascade and induce a thrombogenic state in a similar manner as SIRS. TNF-α and interleukin 1β are released by cancer cells and induce tissue factor expression and down-regulate thrombomodulin. Furthermore, tumor cells activate other cytokines and several different types of leukocytes, which also increase tissue factor expression and activate platelets. The interaction of all these processes lead to a prothombotic condition.[31]

Testing for Inherited Thrombophilic Conditions

We perform testing for inherited thrombophilic conditions in the following clinical circumstances: idiopathic DVT, recurrent DVT, DVT with young age at onset, and venous thromboses in unusual locations (mesenteric or portal venous thrombosis, cerebral vein thrombosis). Many hospitals provide testing with a "hypercoagulable panel." However, the clinician should ascertain that the following tests are being performed: antithrombin activity, protein C activity, protein S activity, testing for either activated protein C resistance or factor V Leiden, prothrombin gene mutation, homocysteine levels, anticardiolipin antibody and lupus anticoagulant testing, factor VIII activity. Antithrombin, protein C, and protein S levels may be depressed by the presence of acute thrombosis. Protein C and S may be similarly affected by warfarin administration. Therefore, an abnormal test result drawn during these time periods does not necessarily signify the presence of an inherited thrombophilic condition. Repeat testing is required.

Other Acquired Hypercoagulable Conditions and Treatment Stratification

Patients are predisposed to thrombosis via many other clinical conditions. These conditions may affect the coagulation cascade, the fibrinolytic system, and/or platelet function, thereby increasing the risk of thrombosis. With two or more conditions that predispose to thrombosis, the patient is at a higher risk for suffering a thrombosis.

The objectives for treating acute venous thromboembolism include the prevention of death from pulmonary embolism, reduction of lower extremity symptoms, prevention of the post-phlebitic syndrome, and prevention of recurrent venous thromboembolism. By limiting the propagation of thrombus, anticoagulation potentially has a role in achieving all of these objectives. Initial anticoagulation with unfractionated heparin or low-molecular-weight heparin, followed by six weeks to six months of oral vitamin K antagonists has been the mainstay of therapy. More recently, the American College of Chest Physicians Consensus Statement has stratified the type and duration of anticoagulation, based in part on the whether the patient has a concurrent thrombophilic condition (see Table 38.4).[32] In general, the overall trend is to extend the duration of anticoagulation, especially in patients with recurrent DVT, antiphospholipid syndrome, and patients with multiple thrombophilic conditions. In patients with malignancy and venous thromboembolism, the recommended duration of low-molecular-weight heparin therapy has been extended to three to six months, followed by long-term vitamin K antagonists.

TABLE 38.4 American College of Chest Physicians Recommendations for Duration of Anticoagulation for Venous Thromboembolism[32]

Clinical subgroup	Treatment duration
First episode DVT/transient risk	UH/LMWH followed by 3 mos VKA
First episode DVT/concurrent cancer	3–6 mos LMWH Indefinite anticoagulation until cancer resolves
First episode idiopathic DVT	UH/LMWH followed by 6–12 mos VKA (suggest indefinite)
First episode DVT/thrombophilia antithrombin deficiency protein C and S deficiency factor V leiden prothrombin 20210 homocysteinemia factor VIII elevation (>90th %)	UH or LMWH followed by 6–12 mos VKA (suggest indefinite if idiopathic)
First episode DVT/thrombophilia Antiphospholipid antibodies 2 or more thrombophilias	UH or LMWH followed by 12 mos VKA (suggest indefinite)
Recurrent DVT	UH or LMWH followed by indefinite VKA

UH = unfractionated heparin, LMWH = low-molecular-weight heparin, VKA = vitamin K antagonist.

CONCLUSION

A clear understanding of the various conditions and situations in which a patient may have a hypercoagulable state is important for the ability to manage and appropriately treat patients in whom the risk of thrombosis exists. Once that risk is recognized, appropriate observation, prophylaxis, and treatment may ensue. It must be recognized that the number of acquired disease processes that predispose patients to thrombosis far outweighs the number of patients with congenital thrombophilias. Although a large portion of the

population may have a thrombosis, few thromboses are caused by an inherited thrombophilia alone.

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C H A P T E R

39

New Ways to Prevent Venous Thromboembolism: The Factor Xa Inhibitor Fondaparinux and the Thrombin Inhibitor Ximelagatran

DAVID BERGQVIST

ABSTRACT

During the last decade low molecular weight heparins have been the dominant methodology to prevent postoperative venous thromboembolism. They are effective and safe but in high risk surgery (major orthopedic and abdominal/pelvic cancer) there is still a significant thromboembolic risk. Recently two new thromboprophylactic agents have been developed—one, a factot Xa inhibitor in the form of the pentasaccharide fondaparinux and the other a direct thrombin inhibitor in the form of melagatran with an orally absorbable prodrug—ximelagatran. Both have been evaluated in extensive research programs and both have been approved for use in major orthopedic surgery by the European health care authorities.

INTRODUCTION

In prevention of postoperative venous thromboembolism, one or another of the low molecular weight heparins has dominated the market for about 15 years. There is, however, still room for improvement, especially in patients undergoing high risk surgery such as major orthopedic surgery and surgery for abdominal/pelvic malignancies. For the clinician and for the patient new methods either should be more effective or safer than low molecular weight heparins, cost-effective or easier to administer (i.e., available for oral administration). The latter is especially true as long-term prophylaxis will undoubtedly increase.

The various low molecular weight heparins have a rather complex mechanism of action, inhibiting activated factor X to a greater degree than inhibiting thrombin. This has been considered necessary for a good prophylactic effect.

Recently, there have been two important developments within the field of antithrombotic agents. One development was to use the heterogenous heparin molecule as a basis, and working with the relation between structure and function Lindahl et al.[1,2] to define the specific antithrombin-binding pentasaccharide sequence. The research group of Choay in Paris was able synthesize thus as fondaparinux—a selective Xa inhibitor.[3,4] The other development was to synthesize small direct thrombin inhibitors, knowing the pivotal role thrombin plays within the hemostatic system and knowing that the thrombin inhibitor hirudin (originally from the saliva of medicinal leeches) had a good thromboprophylactic effect.[5] Many attempts have been made to synthesize such small selective thrombin inhibitors and so far most clinical documentation is available on ximelagatran/melagatran.[6–8]

Those two new principal ways of preventing venous thromboembolism with molecules that are more selective and structurally more homogenous now have been investigated in large clinical trial programs and both have European approval, fondaparinux in major orthopedic surgery and ximelagatran/melagatran in elective major orthopedic surgery.

When evaluating new thromboprophylactic substances and principles in the clinical setting, ideally there should be a three-step research program:

1. Studies on mechanism of action, pharmacokinetics, and pharmacodynamics.
2. Proof of principle with phlebographic evaluation of the antithrombotic effect in high risk
   a. major orthopedic surgery
   b. major abdominal/pelvic surgery (especially cancer)
3. Proof of clinical importance in
   a. large studies with a simple protocol on clinical venous thromboembolism (VTE)
   b. meta-analyses

Regarding step 2, although elective hip surgery is a well-established clinical model, it is important also to evaluate other high-risk surgical procedures. This is to make conclusions and clinical use more generalizible. From a practical point of view it is not ideal to have different prophylactic programs for various surgical procedures in a hospital or a surgical department. Prophylaxis must be simple to obtain widespread and well-accepted use. The manufacturers of the two new substances discussed in this chapter first have focused on major orthopedic surgery and also got European approval in major orthopedic surgery.

FONDAPARINUX

Fondaparinux is a synthetized analogue of the natural pentasaccharide sequence of the heparin molecule, that mediates its interaction with antithrombin.[4] The molecular weight is 1728 Dalton and with a very high batch-to-batch consistency. The reversible binding, to a specific site on antithrombin, results in a 300-fold increase in the rate of factor Xa inhibition by antithrombin. After subcutaneous administration with a 100% bioavailability the peak plasma level is obtained in about 2 h with an elimination half life of about 17 to 21 h, longer in elderly, which allows once-daily administration.[9,10] The elimination is mainly unchanged through the renal route. The drug is contraindicated in patients with renal failure as defined by a creatinine clearance of less than 30 ml/min. If used there is a potential for bleeding complications. A peak steady state plasma level is reached after three to four days (dose 2.5 mg daily). There is no specific antidote to fondaparinux but in case of an emergency recombinant factor VIIa may be used.[11] This would be the case in accidental overdosing with clinical hemorrhage.

A large phase III clinical program has been performed to evaluate the effect of fondaparinux in major orthopedic surgery of the lower limbs. The studies have used various acronyms: EPHESUS (European Pentasaccharide Hip Elective SUrgery Study with 2309 patients[12]), PENTATHLON (PENTAsaccharide in Total Hip Replacement Surgery with 2275 patients[13]), PENTAMAKS (PENTAsaccharide in MAjor Knee Surgery with 1049 patients[14]), and PENTHIFRA (PENTAsaccharide in HIp FRActure surgery with 1711 patients[15]). The studies have been consistently performed using 2.5 mg fondaparinux daily starting postoperatively. The comparator has been enoxaparin: in EPHESUS and PENTHIFRA with 40 mg once daily with a preoperative start as used in Europe and in PENTATHLON and PENTAMAKS with 30 mg twice daily with a postoperative start as used in North America. Phlebography was used for endpoint assessment and the studies have been evaluated in a meta-analysis.[16] The primary efficacy outcome is summarized in Table 39.1, the common odds reduction being 55% in favor of fondaparinux ($p < 0.001$). The incidence of symptomatic VTE was low without a difference between the groups (0.6% in the fondaparinux group and 0.4 in the enoxaparin group; $p > 0.25$). Fatal pulmonary embolism was diagnosed in two and three patients, respectively. The beneficial effect of fondaparinux was consistent regarding sex, age, body mass index, type of anesthesia, use of cement for fixation of prosthesis, and duration of the surgical procedure.

TABLE 39.1 Frequency of Venous Thromboembolism (VTE) Up to Day 11[16] (Percent within brackets)

	Fondaparinux (n = 2682)	Enoxaparin (n = 2703)
VTE	182 (6.8)	371 (13.7)
Any DVT	174 (6.5)	363 (13.5)
Any proximal DVT	35 (1.3)	81 (2.9)

TABLE 39.2 Fondaparinux in High Risk Abdominal Surgery (PEGASUS)[19] (venographic DVT)

	Fondaparinux	Dalteparin
Primary efficacy analyses	47/1027 (4.6%)	62/1021 (6.1%)
Patients with cancer	37/696 (4.7%)	55/712 (7.7%)

There were 2.7% adjudicated major bleedings in the fondaparinux group versus 1.7 in the enoxaparin group ($p = 0.008$). This difference was due mainly to a difference in bleeding index whereas fatal bleeding, bleeding in critical organs, and bleeding leading to reoperation did not differ. There was a significant relation between the incidence of major bleeding and the timing of the first injection of fondaparinux (between 3 and 9 hours postoperatively, $p < 0.008$), whereas the thromboprophylactic effect was not influenced by timing ($p > 0.67$). Thrombocytopenia has not been reported (there is no binding to platelet factor 4).[17]

In PENTHIFRA Plus,[18] the effect of prolonged prophylaxis with fondaparinux has been evaluated in patients undergoing hip fracture surgery. All 656 patients received fondaparinux for six to eight days, thereafter they were randomized to placebo or fondaparinux for another 19 to 23 days. Venous thromboembolism (bilateral phlebography or symptomatic VTE) differed significantly, being 35% in the placebo group and 1.4% in the fondaparinux group, a reduction that is highly remarkable. The effect was also significant when symptomatic VTE was used as endpoint (2.7% vs 0.3%; $p < 0.02$).

In a recent multicenter, double-blind study (PEGASUS trial) on 2048 patients undergoing high risk abdominal surgery, fondaparinux was shown to be noninferior to dalteparin (Agnelli et al.[19]). In the subgroup operated on for malignant disorders the difference was significant in favor of fondaparinux (see Table 39.2).

TABLE 39.3 Design of Orthopedic Studies on Ximelagatran/Melagatran

METHRO II	Dose finding study. Four groups with melagatran 1–3 mg × 2 and then ximelagatran 8–24 mg × 2. Preop start.
METHRO III	Melagatran 3 mg and then ximelagatran 24 mg × 2. Postop start.
EXPRESS	Melagatran 2 mg preoperatively, 3 mg postoperatively, and then ximelagatran 24 mg × 2.
EXULT A	Ximelagatran 24 and 36 mg × 2. Late postop start.
EXULT B	Ximelagatran 36 mg × 2. Late postop start.

Idraparinux is a fondaparinux analogue with modified pharmacokinetics making once weekly administration possible, clinical studies being on the way.[20–22]

XIMELAGATRAN/MELAGATRAN

Ximelagatran is a novel oral direct thrombin inhibitor, which is a prodrug rapidly absorbed in the small intestine and bioconverted to the dipeptide melagatran (429 Da), which is the active form.[23] Melagatran is a selective, competitive small–molecular direct inhibitor of free and clot-bound thrombin with a complete bio-availability on subcutaneous injection. Melagatran is mainly excreted via the kidneys (around 80%).[24] After single and repeated oral dosing of ximelagatran the bioavailability of melagatran is around 20%.[25] Maximum melagatran concentrations are reached in approximately two hours. A similar absorption is also seen three days after abdominal surgery.[26] The main absorption site is the duodenum. Ximelagatran/melagatran has no known food interaction and no clinically relevant drug interactions involving cytochrome P450 enzymes. Ximelagatran is the first oral direct thrombin inhibitor on the market.

In an extensive phase III clinical program ximelagatran has been evaluated in major orthopedic surgery. Again various investigation acronyms have been used: METHRO II (MElagatran for THRombin inhibition in Orthopaedic surgery; hip and knee replacement, 1876 patients, dose finding study, comparator dalteparin with preoperative start[27]), METHRO III (hip and knee replacement, 2788 patients, comparator enoxaparin with preoperative start[28]), EXPRESS (EXpanded PRophylaxis Evaluation Surgery Study, hip and knee replacement, 2835 patients, comparator enoxaparin with preoperative start[29]) in Europe and EXULT A (EXanta Used to Lessen Thrombosis, knee replacement, 2285 patients, comparator warfarin[30]), and EXULT B (knee replacement, 2299 patients, comparator warfarin[31]) in North America. The design of the various studies is summarized in Table 39.3. In METHRO II the efficacy of melagatran/ximelagatran was dose dependent and the highest dose was superior to dalteparin both for total VTE (15.1 vs 28.2%, respectively, $p < 0.0001$) and major VTE (2.5 vs 6.5%, $p < 0.05$). In METHRO III with postoperative start melagatran/ximelagatran was at least as effective as enoxaparin (overall VTE 31 vs 27%), but in hip replacement there was significant difference in favor of enoxaparin for total VTE (25 vs 19%, $p < 0.004$). Initiation of prophylaxis closer (4–8 h) to surgery was significantly more effective than later institution (8–12 h) in prevention of total VTE.[28] In EXPRESS with preoperative start again there was significant advantage for melagatran/ximelagatran in total VTE (20 vs 27%, $p < 0.001$) and major VTE (2.3 vs 6.3%, $p < 0.0001$). In the EXULT A with start the day after surgery the higher dose ximelagatran (36 mg × 2) was more effective than warfarin to prevent total VTE (20 vs 28%, $p < 0.01$), a result that was further verified in EXULT B (23 vs 32%, $p < 0.001$). Regarding major VTE there were no significant differences in the EXULT studies.

Bleeding events and measured blood loss did not differ between ximelagatran/melagatran and the various comparators. In METHRO II there was a significant dose-dependent (from 8 mg to 24 mg) increase in the proportion of patients on ximelagtran/melagatran with severe bleeding. In Table 39.4 the bleeding events in the various studies are summarized.

There is no specific antidote and the effect is limited by the rapid renal clearance. Intravenous activated prothrombin complex or recombinant activated factor VII rapidly attenuates the melagatran effect.[32]

An increase in liver enzymes (ALT, alanine aminotransferase) has been reported in patients receiving long-term (mostly > 35 days) melagatran/ximelagatran.[33] However, in the prophylactic trials with short-term administration (≤11 days) this incidence has been of the same order of magnitude as in the low molecular weight heparin groups. The effect has been reversible. The mechanism responsible for the liver enzyme changes is not yet established.

Trials in nonorthopedic surgery basically are lacking. There is one study primarily focused on pharmacodynamics in patients undergoing major abdominal surgery.[26] In the study on 90 patients venographic DVT was evaluated on the final day of treatment and the results are given in Table 39.5. Although a small study, the DVT frequencies are of the same order of magnitude as in similar studies on low molecular weight heparins. The data are of interest when discussing the possibility of prolonged prophylaxis, which may be of value in patients operated on for abdominal/pelvic cancer.[34] The advantage of an oral drug in this situation seems obvious.

CONCLUDING REMARKS

Today, there are two synthetic substances inhibiting very well-defined steps or specific factors in the hemostatic system, both showing a clear effect in prevention of

TABLE 39.4 Bleeding Complications in Orthopedic Trials with Melagatran/Ximelagatran[35]

European trials	Number of patients in population	Severe bleeding (%)	Total bleeding (%) (severe and minor)
METHRO II (ITT):			
Ximelagatran 8 mg	364	1.1	NA
Ximelagatran 12 mg	377	2.1	NA
Ximelagatran 18 mg	375	2.9	NA
Ximelagatran 24 mg	379	5.0	NA
Dalteparin	381	2.4	NA
METHRO III (ITT):			
Ximelagatran	1399	1.4	NA
Enoxaparin	1389	1.7	NA
EXPRESS (ITT):			
Ximelagatran	1410	3.3	12.5
Enoxaparin	1425	1.2	8.2
North American trials	**Number of patients in population**	**Major bleeding (%)**	**Total bleeding (%) (major and minor)**
Francis et al. (ITT) (22):			
Ximelagatran 24 mg	348	1.7	9.5
Warfarin	332	0.9	7.3
EXULT A (ITT):			
Ximelagatran 24 mg	775	0.8	5.3
Ximelagatran 36 mg	762	0.8	4.8
Warfarin	764	0.7	4.5
EXULT B (OT):			
Ximelagatran 36 mg	1151[§]	1.0	5.0
Warfarin	1148[§]	0.4	3.8

TABLE 39.5 Frequency of DVT According to Phlebography (%) in High-Risk Abdominal Surgery[26]

	Melagatran/ Ximelagatran		
	8 days	35 days	Dalteparin
Intention-to-treat population	13.6	12.0	8.7
Per protocol population	12.5	5.0	10.0

postoperative venous thromboembolism in major orthopedic surgery. Apart from being of practical importance the principal mechanisms of action are of great theoretical interest.

The Xa inhibitor fondaparinux and the direct thrombin inhibitor ximelagatran/melagatran have been evaluated extensively in clinical studies of high quality with large sample sizes. Both substances are at least as effective or more effective than today's dominating prophylactic methods (low molecular weight heparins and warfarin). Still data largely are lacking on prophylaxis in nonorthopedic surgery but the few results seem promising. A second and direct thrombin inhibitor, dabigatran, is in phase II trials in 2005.

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CHAPTER

40

Diagnosis of Deep Vein Thrombosis

WARNER P. BUNDENS

BACKGROUND

Patients with one or more of Virchow's triad of stasis, hypercoagulability, or vein wall abnormalities are susceptible to thrombosis.[1] Lower limb deep venous thrombosis (DVT) is a common and potentially serious problem. Over five million occur in the United States annually, and approximately 10% become pulmonary emboli.[2,3] Ninety percent of pulmonary emboli originate from lower limb DVTs.[4,5] DVT can also result in permanent venous obstruction (i.e., chronic DVT) and/or damage to venous valves leading to post-phlebitic chronic venous insufficiency. Timely and accurate diagnosis can aid significantly in the reduction of morbidity and mortality.

The clinical presentation of DVT can range from silent, with no symptoms or physical findings, to phlegmasia cerula dolens and venous gangrene. The sensitivity and specificity of symptoms and physical findings such as pain, tenderness, swelling, redness, or a positive Homan's sign range from 30 to 80%. The clinical diagnosis of DVT is not reliable with an overall accuracy of only approximately 50%.[6–10] Thus, when DVT is suspected or part of a differential diagnosis an accurate, objective test that can rule in or rule out DVT is indicated.

Though this chapter is devoted to the diagnosis of thrombosis in the deep leg veins, one should keep DVT in mind when seeing a patient with superficial thrombophlebitis. The clinical diagnosis of thrombophlebitis of a superficial vein is accurate. One should be aware, however, that multiple studies have shown that approximately 20% of patients will also have an occult DVT.[11–16] The extent of thrombus in superficial veins usually extends further than is evident clinically and in up to one third of cases the thrombus eventually will extend into the deep system via the saphenofemoral junction or communicating veins.[17–19]

The traditional gold standard of objective DVT testing is ascending contrast phlebography. Compared to autopsy findings it has a 97% sensitivity and 95% specificity.[20] The test, however, is costly, invasive, uncomfortable, and associated with definite risks. One of the "particularly unwelcome" complications is a 2 to 3% risk of the contrast agents actually causing DVT.[9] For decades the trend has been to less invasive and, in the case of ultrasound, less expensive methods of studying patients suspected of having DVT. For years radioactive fibrinogen scanning and impedance plethysmography were widely used have been supplanted by duplex ultrasonography as scanners became widely available and multiple studies showed acceptable accuracy. Currently duplex ultrasonography is still the most commonly used method of testing for lower limb DVT though other methodologies are being used increasingly in selected settings.

DUPLEX ULTRASONOGRAPHY

The combination of B-mode imaging and the pulse Doppler into one instrument, the duplex, was originally done as an aid to arterial diagnosis. It soon became evident that it also could be used for venous investigations of both obstruction and reflux. Over the past 25 years the hardware technology has improved the quality of the B-mode imaging dramatically. Color-coded flow displays as well as "power Doppler" are now available in most instruments. These two modes are often helpful for locating veins, and outlining intraluminal defects.

TABLE 40.1 Duplex Findings of Lower Limb DVT

Mode	Finding	Implication
B-Mode Image	Unable to coapt vein walls with probe pressure	Intraluminal thrombus
	Visible thrombus	Thrombus, possibly old
	Vein enlarged	Acute thrombus
Pulse Doppler	No spontaneous flow	Occlusive thrombus
	No augmentation of flow with distal limb compression	Obstruction distal to probe
	No flow variation with respiration	Obstruction proximal to probe
Color Flow or Power Doppler	Intraluminal defect	Nonocclusive thrombus
Combined	Increased flow velocity and size of surrounding veins	Being used as collaterals

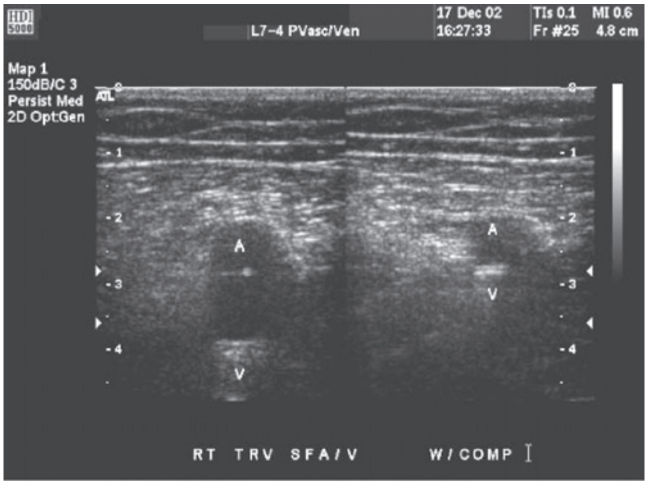

FIGURE 40.1 Duplex of normal femoral vein. Vein can be completely collapsed with probe pressure.

The possible duplex findings of a lower limb DVT are listed in Table 40.1. Virtually all vascular labs use the first criteria, the inability to collapse a vein with probe pressure (Figures 40.1 and 40.2), as the primary diagnostic method. Some use only this finding.[21] Meta-analysis has shown this sign to be 95% sensitive and 98% specific for proximal leg DVTs. When all the criteria of Table 40.1 are used the sensitivity is 98% and specificity 94%.[22]

Though the accuracy of this noninvasive, readily available, and relatively low-cost test is impressive one should realize most data reflect findings in patients with femoral and/or popliteal vein disease. The majority of patients with symptomatic DVTs have thrombus in these veins.[23,24] In some cases the thrombus also may involve the iliac or calf veins. Duplex examination may not detect the full extent of thrombosis in these instances but at least the diagnosis of

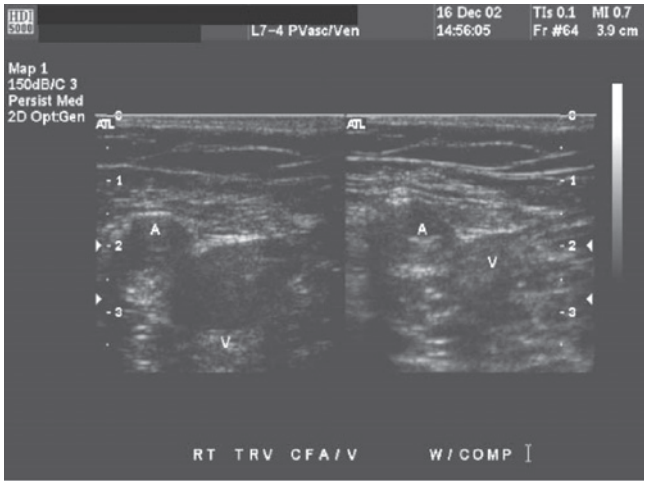

FIGURE 40.2 Duplex of acute femoral vein DVT. Vein cannot be collapsed with probe pressure. Also note, vein is enlarged and thrombus is echolucent and partially compressible, which are signs of acute thrombus.

DVT will be made and presumably appropriate treatment given. One must realize, however, that isolated calf vein DVTs are common, and isolated iliac thrombi do occur. Duplex is not as accurate in these instances. In a study of postoperative orthopedic patients, 24% of the symptomatic and 88% of the asymptomatic patients had isolated calf thrombi. In the symptomatic group duplex was 85% sensitive and 86% specific, but in the asymptomatic group sensitivity was 16% and specificity 99%.[25]

Isolated iliac vein thrombosis often is reported as being rare. However, most series from which data come do not include patients who are at increased risk for this problem, such as those who are pregnant, or have pelvic conditions such as tumors, trauma, or recent surgery. The true incidence of isolated pelvic vein thrombosis is unknown but probably higher than previous estimates. Most vascular labs do not routinely scan iliac veins as part of a lower extremity DVT study. Those that do find the study unsatisfactory because of excessive bowel gas in 20% of patients.[26] The primary sign used in the leg, the ability to coapt vein walls with probe pressure, is usually not possible. Many labs use indirect signs such as lack of flow variation with respiration in the proximal femoral ("common femoral") vein, or a 50% increase in proximal femoral vein diameter with the Valsalva maneuver. The accuracy of these methods varies greatly in the literature.[27–30] Magnetic resonance venography is a more reliable diagnostic modality in these patients (see later).

In addition to the ability to diagnose the presence of a deep vein thrombosis, duplex ultrasonography usually provides information as whether the thrombus is acute or chronic. Criteria are listed in Table 40.2. The finding of a partially compressible thrombus is the most common reliable sign of an acute DVT. A "free floating" thrombus; that is, thrombus that appear to be moving within the vein lumen

TABLE 40.2 Duplex Criteria for Differentiating Acute versus Chronic Thrombus (Modified from Karkow, Ruoff, and Cranley. B-Mode Imaging, in Practical noninvasive vascular diagnosis. 1982.)

Characteristic	Acute		Chronic	
Degree of Occlusion	Total	++	Partial	++
Free Floating	Free	++++	Stationary	+
Clot Compressibility	Soft	++++	Firm	+
Surface Character	Smooth	++	Irregular	++
Echogenicity	Faint or None	++	Bright	++
Homogeneity	Homogen.	++	Heterogen.	++
Collaterals	Absent	+	Present	++
Recanalization	Absent	+	Present	++++

++++ = Diagnostic, +++ = Good, ++ = Fair, + = Poor

TABLE 40.3 Sensitivity and Specificity of Different D-dimer Tests (Figures represent averages from the literature.[35–38] The results include subjects with both possible pulmonary embolism and/or DVT.)

Method	Sensitivity (%)	Specificity (%)
ELISA	96	39
Red Blood Cell Agglutination	88	64
Latex Agglutination	87	60

are seen only occasionally. Many clinicians use the criteria of the degree of echogenicity of a thrombus to determine age. Although the echogenicity of thrombus does increase with time, it is also dependant on the duplex settings and is only a fair indication of age.[31–34]

Determination of the thrombus age is particularly important when a clinician is faced with the presentation of a patient with a past history of DVT who presents with the complaint of new or increasing leg pain and/or swelling with no past studies available for comparison. Because 10 to 20% of acute DVTs may become chronic, determining if the patient has a new thrombus, or new thrombus in addition to chronic thrombus or some other cause of the leg symptoms such as chronic venous insufficiency can be challenging. When thrombus is found, application of the age criteria in Table 40.2 are reliable but one should realize there may be both acute and chronic thrombi in conjunction—that is, “new on old.” In these cases one should look for partially compressible thrombus (i.e., acute) at either the proximal or distal ends of the old DVT.

Duplex examination also can be used to help determine the cause of leg pain and/or swelling when a DVT is not found. Intramuscular hematomas (sometimes with associated muscle tears), ruptured and unruptured Baker’s cysts, and venous reflux disease are common causes of symptoms that may mimic DVT and often can be identified by duplex ultrasound if one keeps them in mind.

D-DIMER

The use of a blood test to rule in or rule out DVT, and negate the need for more complicated and expensive testing, has received considerable attention in the last decade as monoclonal antibody tests have become available to detect circulating D-dimer. D-dimers are degradation products that result from the action of plasmin on cross-linked fibrin. Thus the presence of D-dimer is an indication of the initiation of blood clotting. Unfortunately numerous conditions other than DVT can give positive D-dimer test results.

Several laboratory methods are currently available for D-dimer testing (see Table 40.3). Though the enzyme-linked immunosorbent assay (ELISA) is the most sensitive it is also the most expensive and time consuming. The others are less expensive and much quicker, taking minutes as opposed to hours, and are thus more attractive as clinical tools for management of patients with suspected DVT. As can be seen from the table, however, the low specificity makes a positive test virtually useless for ruling in DVT. Infection, inflammation, vasculitis, pregnancy, trauma, hemorrhage, and post-surgical states can cause a positive D-dimer test.

A negative test may be a useful aid in ruling out DVT. Numerous studies have reported sensitivities of D-dimer but different methodologies are used, populations tested vary, and many studies combine patients with pulmonary emboli and/or DVT. Other studies have shown varying sensitivity in relation to the timing of testing and to the location and or extent of DVT.[35–38]

Though Wells et al. showed that anticoagulation could safely be withheld in patients with a low clinical suspicion of DVT and a negative D-dimer test these results should not be generalized unless one knows the methodology and accuracy of the laboratory used.[39] Until there is standardization of D-dimer testing and better information on the negative predictive value of the test in heterogenous populations one should not rely solely on a negative D-dimer result to rule out DVT.

MAGNETIC RESONANCE VENOGRAPHY

The quality of magnetic resonance venography (MRV) has steadily improved since its introduction in the early 1990s. It is now a powerful technology that often is used as a problem solver. Various techniques are used, including spin echo and gradient recalled echo. Intravenous gadolinium can be used to enhance images and can aid in determination of the age of the thrombus. Absence of imaging of a vein or an intraluminal filling defect indicate the presence of DVT. Examiners must be cognizant, however, of known

flow artifacts that can be mistaken for thrombus. Images can be viewed in axial, coronal, or sagittal planes and post-processing techniques are available that can be used to produce 3D images with removal of background structures for improved ease of viewing.

MRV has been shown to be highly accurate. Sensitivities of 97% and specificities of 100% have been demonstrated along with excellent interobserver variability for iliac, femoral, and below knee DVT.[40,41] Several authors now consider MRV to be the study of choice for pelvic vein DVT. Compared to conventional contrast venography it is not only noninvasive and avoids the use of ionizing radiation, but it also has demonstrated better ability to show the proximal extent of femoral and iliac vein thrombi. An added advantage is that it may show underlying pathology that contributed to the formation of the DVT such as pelvic masses or left iliac vein compression by the right common iliac artery.[42]

The limitations of MRV include expense, lack of portability, and in some cases, availability. Also, some patients with implanted metal devices, claustrophobia, and inability to remain still are not suitable for this exam.

COMPUTERIZED TOMOGRAPHIC VENOGRAPHY

Computerized tomographic venography has many of the same advantages as MRV when compared to duplex ultrasound. It does involve, however, the use ionizing radiation and for imaging peripheral veins the use of intravenous iodinated contrast agents. In imaging peripheral and pelvic veins the accurate timing of image acquisition in relation to contrast injection is often difficult and multiple runs may be necessary to acquire all the desired veins. In larger veins one can also be faced with the inflow of noncontrast blood from a branch vein into a vein with blood containing contrast, which creates a "wash in" artifact that can be mistaken for thrombus. For these reasons MRV usually is considered a more appropriate modality when duplex testing is felt to be inadequate. However, some do employ a technique known as combined computerized tomographic venography and pulmonary arteriography (CCTVPA). Computerized tomographic pulmonary arteriography (CTPA) has become the test of choice in many centers for suspected pulmonary emboli. Katz et al. has reported that by waiting for 3 to 3.5 minutes after the injection of contrast that is used for CTPA, one can then scan the veins from the diaphragm to the calves. The scanning can be a survey with cuts taken every 4 cm or as a continual helical imaging. This test does involve considerably more radiation to the subject, however.[43] Thus, with this technique, one study can not only answer the question of whether or not there is a pulmonary embolus and its extent, but also often find the source of the embolus and the amount of residual thrombus in the veins. Ninety-seven percent sensitivity and 100% specificity has been reported in comparison to ultrasound and a large study has shown that in patients with lower limb DVT, 23% extended into the iliac veins or the inferior vena cava.[44]

SUMMARY

It is well documented that the clinical diagnosis of lower limb DVT is unreliable. Fortunately there are a number of methodologies available that can objectively rule in or rule out the presence of DVT with accuracies very close to the gold standard of conventional contrast phlebography. They are also less invasive, safer, and usually less costly. This chapter has presented a brief overview of the currently available technologies that continue to evolve and improve. The limitations and shortcomings of the present day testing methods should be viewed as challenges and not barriers to improving patient care.

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CHAPTER

41

Thrombotic Risk Assessment: A Hybrid Approach

JOSEPH A. CAPRINI

INTRODUCTION

Venous thromboembolism (VTE) is one of the most common, yet highly preventable causes of in-hospital death. In response to this problem, the implementation of an appropriate, targeted thromboprophylaxis strategy has been described as the most important single factor for improving patient safety.[1] Both medical and surgical patients are at risk of VTE. It has been calculated that without prophylaxis, the incidence of hospital-acquired deep vein thrombosis (DVT) is approximately 10 to 40% among medical or general surgery patients, and 40 to 60% following major orthopedic surgery.[2] Approximately 10% of all deaths in the hospital subjected to autopsy are attributed to pulmonary embolism (PE),[3] with most patients who suffer a fatal embolus dying within the initial 30-minute period. This small window for effective treatment, combined with its frequently asymptomatic nature, explains the high fatality rate associated with this condition.[4] VTE is also responsible for a significant number of long-term health problems: 30% of patients with symptomatic DVT will suffer recurrent VTE in the following eight years,[5] and Prandoni has shown that almost a third of patients who suffer a DVT will go on to develop long-term venous insufficiency complications in the lower leg, also known as *postthrombotic syndrome* (PTS). This condition may result in chronic leg swelling, discomfort, dermatitis, and leg ulcers, which can reduce the patient's quality of life and have an economic impact frequently overlooked in DVT cost assessment.[6]

Clinically proven methods of prophylaxis have been shown to prevent a significant proportion of clinically significant VTEs. Yet despite the publication of regularly updated consensus guidelines,[2,7–10] VTE prophylaxis is still under- or inappropriately prescribed in a high proportion of patients, leaving them at significant risk of serious complication due to PE or DVT.[11,12]

Effective VTE risk assessment is therefore critical in targeting and optimizing prophylaxis, and for the subsequent improvement in patient outcomes. There is an urgent need for a clear, easy-to-use risk assessment model based on information in the patient's medical history and clinical examination. Although there has been, and continues to be, a great deal of clinical research into VTE, it is unlikely that there will ever be sufficient high-quality clinical evidence to guide decisions on prophylaxis in every group of patients—medical and surgical. With each patient representing a unique clinical situation with their own combination of risk factors, it can be difficult to determine the level of VTE risk, and the appropriate intensity of thromboprophylaxis. This review considers the reasons contributing to underuse of prophylaxis, and discusses a hybrid approach, combining risk assessment scoring with the application of current treatment guidelines. The results of an audit from the author's hospital and a real-world case study are also detailed to illustrate key issues.

POOR ADHERENCE TO PROPHYLAXIS GUIDELINES

Consensus groups such as the American College of Chest Physicians (ACCP) and the THRIFT Consensus Group regularly publish guidelines on the prevention and treatment of VTE in both surgical and nonsurgical patients.[2,7–10] Although the recommendations from these groups are based on clinical evidence from trials and meta-analyses that are stratified clearly according to patient risk, VTE prophylaxis is still

suboptimal in many patients,[11–17] and the rates of total and proximal DVT remain high.

US surveys of prophylaxis use indicate that the percentage of surgical patients receiving prophylaxis ranges from 38 to 94% according to the type of procedure.[11,15,18,19] One particular study documenting adherence to the 1995 ACCP guidelines in surgical patients found that 25% of patients undergoing high-risk major abdominal surgery did not receive any form of VTE prophylaxis.[11] Furthermore, in a retrospective analysis by Arnold et al. looking at cases of VTE in a US cohort of surgical and medical patients, it was found that one out of six VTE events could have been prevented if physicians had followed the ACCP guidelines.[12] Inadequate prophylaxis was most often due to the fact that no prophylactic measures were prescribed.

Surprisingly, a tendency has been reported for prophylaxis to be administered less frequently with increasing risk level.[20] Why this occurs is unknown, although it may reflect physician concerns that the risk of complications due to anticoagulant therapy may be greater in very high-risk patients.

SUBOPTIMAL PROPHYLAXIS IN ACTION

The extent of the prophylaxis problem was highlighted in a recent study by the author's group.[14] Carried out to test the performance of current VTE risk assessment, the primary objective was to determine the percentage of a surgical patient population falling into one of three risk categories (moderate, high, and highest risk; see Table 41.1). The study also sought to identify whether patients were receiving appropriate prophylaxis based on their risk level, and to compare the degree of compliance with prophylaxis guidelines with that found and reported for the same hospital in 1991. A total of 157 patients undergoing neurosurgery, cardiovascular surgery, general, gynecological, or orthopedic surgery (other than arthroplasty) were included in the study. Each patient had a detailed preoperative VTE risk assessment, and the type and duration of prophylaxis prescribed to each patient was recorded and compared with their individual risk score. In-hospital outcomes for all patients were carefully monitored, and patients were followed up by telephone after a month.

The study found that 19% (30 of 157) of patients were not prescribed any prophylactic measures despite the existence of several risk factors. This was even more surprising considering that the majority of patients were in the highest risk category, and therefore at greatest need of prophylaxis. Clinically overt VTE appeared in two out of 73 (2.7%) patients in the highest risk category, both of whom had not received appropriate prophylaxis, and a total 57% of patients were shown to have received inadequate prophylaxis according to the ACCP guidelines.[2] Comparison of these results with our previous thromboprophylaxis audit performed in 1991 (see Table 41.1) indicates no improvement in compliance with treatment guidelines; indeed, in the group at highest risk of VTE, only 30% of patients received appropriate prophylaxis in 2002 compared with 70% in the same category in 1991.

UNDERUSE OF PROPHYLAXIS—WHY IS THERE A PROBLEM?

Misconception of Risk

Although the serious implications to health are now well accepted—both in the short and long term—a large part of the problem can be attributed to its clinically silent nature. For surgical patients there is a low incidence of clinically apparent VTE in the perioperative period, thus it is rare for an individual surgeon to witness an acute PE or major DVT event in one of their patients. Studies have shown that a significant proportion of symptomatic thromboembolic complications occur after discharge from hospital,[21–23] with a survey of California orthopedic surgeons finding that 76% of VTE events were diagnosed following discharge from hospital after total hip replacement (THR), and 48% after

TABLE 41.1 Adherence with ACCP Consensus Guidelines: An Audit of Hospital Practice

	Moderate risk (2 risk factors)	High risk (3–4 risk factors)	Highest risk (5 or more risk factors)
Total (2002)	9/157 (6%)	43/157 (27%)	105/157 (67%)
Prophylaxis guidelines followed	7/9 (78%)	28/43 (65%)	32/105 (30%)
Prophylaxis guidelines not followed	2/9 (22%)	15/43 (35%)	73/105 (70%)
	Low (0–1 risk factors)	**Moderate (2–4 risk factors)**	**High risk (more than 4 risk factors)**
Total (1991)	185/538 (34%)	261/538 (49%)	92/538 (17%)
Prophylaxis guidelines followed	18/185 (10%)	110/261 (42%)	70/92 (76%)
Prophylaxis guidelines not followed	167/185 (90%)	151/261 (58%)	22/92 (24%)

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total knee replacement (TKR).[24] The current trend toward shorter hospital stays serves to accentuate this problem, whereby the need for and benefits of thromboprophylaxis can be difficult to appreciate for a physician who rarely sees the problem. Extended prophylaxis not only has value in preventing sudden death but in prevention of all the other complications of VTE responsible for significant morbidity and mortality.

Although the majority of trials in VTE have studied surgical patients, medical patients are also at significant risk of thrombotic disease.[2] Fewer than a third of patients who suffer a fatal PE recently have undergone surgery,[25] and as many as one in 20 hospitalized patients with multiple clinical conditions go on to develop PE.[26] The average overall incidence of DVT in medical patients is 10 to 20%,[2] but this rises in certain patient groups. For example, stroke is associated with a 20 to 50% risk of VTE complications without prophylaxis,[2] whereas VTE is thought to occur in 20 to 40% of patients with an acute myocardial infarction.[27] Cancer is also a well-known thrombotic risk factor due to the hypercoagulable state induced by the malignancy, with treatments for the disease, such as surgery and chemotherapy, only serving to further compound the risk.[2,28] Despite current guidelines stating that medical patients can be at significant risk of VTE and should receive thromboprophylaxis, a survey from the International Medical Prophylaxis Registry On Venous Thromboembolism (IMPROVE) of acutely ill medical patients recently revealed that fewer than 40% of patients enrolled in the registry received prophylaxis.[13]

Safety Concerns

Another factor underlying the suboptimal use of pharmacological prophylaxis is the overestimation of bleeding risk associated with anticoagulant prophylaxis. For example, a survey of orthopedic surgeons in the United Kingdom found that almost half (48%) had discontinued the use of low molecular weight heparin (LMWH) for TKR or THR due to concern over bleeding complications.[29] However, numerous randomized, placebo-controlled, double-blind trials and further meta-analyses of prophylaxis with LMWH and unfractionated heparin (UFH) during major surgery have demonstrated that both types of heparin prophylaxes are extremely effective in preventing VTE at the expense of no, or a very small, increase in the rate of major bleeding.[30–35] Although LMWH and UFH are associated with an increased risk of wound hematomas,[30,33,34] major bleeding complications are extremely uncommon, and the consequences of VTE are potentially much more severe—thereby outweighing any justification for withholding heparin prophylaxis.

LMWH is at least as safe and effective as UFH.[31,34,54] LMWH has been associated with a lower risk of major bleeding complications; one particular study of patients undergoing abdominal surgery reported a 23% reduction in the frequency of major bleeding events in patients who received LMWH compared with UFH, although this difference was not significant. The study also observed significantly fewer severe bleeds and wound hematomas.[30] LMWH exhibits minimal binding with plasma proteins, endothelial cells, and platelet factor IV, providing a more predictable clinical response than UFH and reduced likelihood of causing heparin-induced thrombocytopenia (HIT).[36,37] With an incidence of 1 to 5%, immune HIT is an uncommon but serious complication of heparin therapy, and often is cited as a reason for caution in prescribing heparin prophylaxis. Of 665 patients who received prophylaxis with either UFH or LMWH during elective THR, 18 patients developed HIT, and the majority of these patients were in the UFH group (4.8% versus 0.6%; $p < 0.001$).[37]

Although the benefits of LMWH thromboprophylaxis have been shown in numerous studies, suboptimal use may arise from additional safety fears combined with a misconception of risk. Clinical issues remain unanswered and may contribute to physician hesitation to pharmacologic prophylaxis; for example, optimal dosing and need for monitoring in patients with severe obesity or renal insufficiency.[2]

Lack of Awareness of the Problem

Physicians frequently cite informal, retrospective surveys of their own clinical service, or personal experience as to why they believe the rate of VTE is low.[38] There also appears to be poor awareness of the diverse range of clinical signs and symptoms that can be attributed to thrombosis and the fact that these relatively minor symptoms can be extremely common (see Table 41.2). Many physicians fail to realize that what they are seeing may be an indicator of an otherwise

TABLE 41.2 Clinical Signs, Symptoms, or Events That May Be Associated with Venous Thromboembolism in Clinical Practice

- Leg pain
- Leg swelling
- Chest pain
- Shortness of breath
- Transient orthostatic hypotension
- Decreased level of consciousness presumed to be narcotic excess
- Fainting spell
- Hypoxia
- Follow-up of patient for readmission or death 90 days postoperatively
- Sudden death
- Death without autopsy
- Postoperative stroke due to patent foramen ovale
- Suspected myocardial infarction
- Failure to thrive, sinking spell or “the dwindles”
- Postthrombotic syndrome during physical examination of the legs (standing) 5 years postoperatively
- Postoperative pneumonia

silent thrombotic event requiring further investigation, which can therefore be attributed to a lack of prophylaxis.

Cost of Suboptimal Prophylaxis

Pharmacological prophylaxis undoubtedly incurs a significant cost, both in terms of the drugs themselves and, with UFH and oral anticoagulants, an increase in nursing time and laboratory monitoring. However, the economic consequences of withholding prophylaxis are often overlooked. In addition to the short-term costs of delayed hospital discharge due to an acute VTE event or patient readmission for DVT, failure to prevent VTE increases the risk of long-term morbidity due to PTS and recurrent thrombosis. Patients with symptomatic DVT have a high risk of recurrent VTE that persists for at least eight years, and that may increase with comorbidities such as cancer.[5] Estimates based on a recent cost-of-illness study conducted by our group suggest that in the United States, the annual per-patient cost of severe PTS is $3816 in the first year and $1677 thereafter, and the cost of DVT and PE complications were estimated at $3798 and $6604, respectively.[39] Therefore, prevention of DVT can have an enormous impact on both the patient's quality of life and the long-term cost of care.

Mechanical methods of prophylaxis provide a cheaper alternative to pharmacological methods taken on a direct cost-per-patient basis, but this must be balanced with issues of safety and efficacy. Mechanical devices, such as intermittent pneumatic compression (IPC) and graduated compression stockings (GCS), do not increase the risk of bleeding and can offer important protection in some groups of patients for whom anticoagulant therapy is contraindicated or is impractical due to their clinical status (e.g., trauma patients). One early study comparing five methods of thromboprophylaxis found that antistasis modalities performed well compared to the drug modalities (UFH, dextran, and aspirin), with the lowest incidence of DVT events reported in the IPC group.[50] A subsequent study evaluating the effectiveness of combining a pharmacologic drug with an antistasis modality reduced the incidence of DVT to just 1.5% in a group of 328 surgical patients.[49] The value of combination therapy has been further highlighted in the more recent APOLLO trial, which compared the use of IPC plus fondaparinux with IPC alone in 1300 high-risk abdominal surgery patients in North America.[58] IPC was chosen on the basis of a survey that found approximately half of clinicians in the United States use this modality for the prevention of thrombosis in general surgery patients. IPC showed 5% incidence of DVT by venograph—therefore by itself an effective modality. IPC plus fondparinux reported a 1.7% incidence. A benefit also is suggested when mechanical methods are combined with LMWH.[2] In a review of trials comparing the use of GCS alone or in combination with LMWH in high-risk surgical patients (general and orthopedic), combination therapy was found to be more effective than pharmacological methods alone.[40]

Overall, however, mechanical means of prophylaxis have been less extensively studied than pharmacological methods, and generally are considered less efficacious than anticoagulants for the prevention of DVT. Although there is evidence supporting their efficacy in low-risk patients,[2] mechanical devices do not provide adequate prophylaxis in those at high-risk. The most recent ACCP guidelines recommend combination therapy for high-risk patients with multiple risk factors, and that, in general, mechanical prophylaxis be used primarily in patients who are at high risk of bleeding or as an adjunct to anticoagulant-based prophylaxis.[2]

The Biggest Problem: Lack of Clear Data?

There are established international guidelines based on level-1 evidence that estimate the incidence of VTE in various populations, and then assess in as scientific a way as possible the efficacy and safety of prophylactic methods based on sound prospective randomized trials. However, only a small subset of what is done in medicine has been tested in appropriate, well-designed studies. Appropriate trials for every clinical situation have not been, and probably never will be, carried out for every situation.

When clinical data are lacking or insufficient to guide treatment, the physician has to use clinical reasoning to identify the approach that best fits the patient and the pathology involved. It can be frustrating to see patients not being given effective prophylaxis simply because there are no data available. Such individuals may be at very high risk of a thrombotic event, but there is no clear treatment path because their clinical situations have yet to be subjected to randomized prospective trials. So how do we ensure such patients are treated appropriately?

MATCHING RISK WITH PROPHYLACTIC STRATEGY

Routine screening of patients for symptomatic DVT is logistically difficult, and both clinically and economically inefficient.[2] Equally, reliance on clinical surveillance to identify early symptoms or signs of DVT is inadequate to prevent clinically important VTE events: the first manifestation of VTE may be a fatal PE.

Thrombotic risk assessment allows patients to be stratified according to their overall VTE risk and thromboprophylaxis to be tailored appropriately, but it is a complex task that must take into account both *exposing* risk factors relating to the clinical situation (e.g., duration/type/site of surgery, type of anesthesia, concomitant illness, presence of infection, etc.), and *predisposing* factors unique to the individual patient (e.g., age, thrombophilic abnormalities, history/

family history of DVT, etc.). Many patients have more than one VTE risk factor and are considered to be at increased risk due to their cumulative effect[41–43] (although interestingly, a recent paper from the MEDENOX study reported an insignificant relationship between the number of VTE events and the number of risk factors).[44] Risk assessment models (RAMs) have been developed with the intention of simplifying and standardizing the scoring of VTE risk, and to allow optimization of prophylactic strategies. Unfortunately, there has been a history of poor compliance with RAMs, with a common complaint from physicians being that they are overly complicated and logistically difficult to implement in their own clinical setting. Many early VTE risk-scoring systems also relied on diagnostic information not readily available from clinical examination (e.g., laboratory values such as euglobulin lysis levels), which has led to reluctance among many doctors to implement such systems.

A simple, clinically validated, easy-to-use RAM based on factors in the patient's medical history and clinical examination is needed, and has the potential to be widely adopted. The model should be used to stratify patients according to risk and the treatment strategy applied in conjunction with academic guidelines where available; that is, the hybrid approach to risk assessment.

A RAM developed by our team and implemented in our hospital overcomes the complexities and practical constraints associated with previous models (see Table 41.3).[45] The model includes clear lists of risk factors with a simple accompanying scoring system, which allows patients to be assigned to one of the four VTE risk categories identified in the ACCP guidelines (low, moderate, high, very high), and

TABLE 41.3 Example of a Practical, Easy-to-Use VTE Risk Assessment Model

Thrombosis risk factor assessment
Patient's name: _____ Age: _____ Gender: _____ Weight: _____

Each factor represents 1 point:
- ❑ Age 41 to 60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (<1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > $25\,kg/tm^2$)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (<1 month)
- ❑ Sepsis (<1 month)
- ❑ Serious lung disease including pneumonia (<1 month)
- ❑ Abnormal pulmonary function (chronic obstructive pulmonary disease)
- ❑ Medical patient currently on bed rest
- ❑ Other risk factors (specify)

Each factor represents 2 points:
- ❑ Age 60 to 74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (>45 minutes)
- ❑ Laparoscopic surgery (>45 minutes)
- ❑ Patient confined to bed (>72 hours)
- ❑ Immobilizing plaster cast (<1 month)
- ❑ Central venous access catheter

Each factor represents 3 points:
- ❑ Age > 75 years
- ❑ History of DVT/PE
- ❑ Family history of thrombosis*
- ❑ Positive Factor V Leiden
- ❑ Positive prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia
- ❑ Other congenital or acquired thrombophilia

If yes, enter type: _________________________
*Most frequently missed risk factor

Each factor represents 5 points:
- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis, or leg fracture (<1 month)
- ❑ Stroke (<1 month)
- ❑ Multiple trauma (<1 month)
- ❑ Acute spinal cord injury (paralysis) (<1 month)

For women only (each factor represents 1 point):
- ❑ Oral contraceptives or hormone-replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent abortion (≥3), premature birth with toxemia or growth-restricted infant

TOTAL RISK FACTOR SCORE ______________________

Prophylaxis safety considerations: Check box if answer is YES
Anticoagulants: Factors associated with increased bleeding
- ❑ Is patient experiencing any active bleeding?
- ❑ Does patient have (or has had history of) heparin-induced thrombocytopenia?
- ❑ Is patient's platelet count <100,000/mm^3?
- ❑ Is patient taking oral anticoagulants, platelet inhibitors (e.g. nonsteroidal anti-inflammatory drugs, clopidogrel)
- ❑ Is patient's creatinine clearance abnormal? If yes, please indicate value.

If any of the above boxes are checked, the patient may not be a candidate for anticoagulant therapy and should consider alternative prophylactic measures.

Intermittent pneumatic compression
- ❑ Does patient have severe peripheral arterial disease?
- ❑ Does patient have congestive heart failure?
- ❑ Does patient have an acute superficial/deep vein thrombosis?

If any of the above boxes are checked, the patient may not be a candidate for intermittent compression therapy and should consider alternative prophylactic measures.

TABLE 41.4 Prophylaxis Decision-Making Tool (based on VTE risk scores)

Total VTE risk score	Incidence of DVT (%)	Risk level	Recommended prophylactic regimen	Risk of fatal PE without prophylaxis (%)
0–1	<10	Low	No specific measures; early ambulation	<0.01
2	10–20	Moderate	LWMH (≤3400 once daily) or LDUH, (5000 U bid) or GCS* or IPC	0.1–0.4
3–4	20–40	High	LMWH (>3400 U daily), LDUH (5000 U tid) or oral anticoagulant alone *or* in combination with GCS or IPC	0.4–1.0
≥5	40–80	Highest	LMWH (>3400 U daily) or LDUH (5000 U tid) or oral anticoagulant alone *or* in combination with GCS or IPC	0.2–5

*Combining GCS with other prophylactic methods (LDUH, LMWH, or IPC) may give better protection.

The total risk score guides the physician to the most appropriate prophylactic treatment; risk categories correspond to the ACCP guidelines.[2]

bid, twice daily; DVT, deep-vein thrombosis; GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LDUH, low-dose unfractionated heparin; LMWH, low molecular weight heparin; PE, pulmonary embolism; tid, three times daily; VTE, venous thromboembolism.

Modified with permission from CHEST.[2]

an appropriate prophylaxis regimen to be recommended (see Table 41.4). The following case study highlights the value of a simple RAM in determining the prophylactic action required for a patient whose risk of VTE is not easily categorized according to current guidelines.

Case Study

Patient History

A 65-year-old man with a body mass index (BMI) >30 kg/m², who received irradiation treatment for prostate cancer five years earlier, was found to have a 2 cm³ carcinoma of the cecum during routine colonoscopy. The patient had been suffering from inflammatory bowel disease for many years and has a parent with a history of documented venous thrombosis who tested positive for both heterozygous factor V Leiden and prothrombin 20210A. The patient also had these thrombophilic defects but had never suffered a thromboembolic event. The patient required a laparoscopically assisted colon resection lasting 2 h 30 min. The patient did well postoperatively and was discharged six days later.

There are no specific data based on prospective randomized trials on VTE risk and prophylaxis in a group of individuals with this combination of risk factors. That is not to say there are no relevant data because it is known that age > 60 years, BMI > 30 kg/m², family history of VTE, inflammatory bowel disease, a history of cancer, and multiple thrombophilic defects are all risk factors for the patient developing a VTE.[2] Should this patient receive thromboprophylaxis given his risk factor profile?

Treatment

During the operation, the patient was protected with pneumatic compression devices to improve circulation in the legs. In addition, a prophylactic LMWH was administered daily for a month starting 12 to 24 hours postoperatively. No complications were reported.

This approach may be considered extreme, and is endorsed at the present time only by a minority of physicians in the United States and worldwide.

So what is the clinical basis of this treatment strategy?

LINKING THERAPY AND RISK

Based on clinical research to date, a patient undergoing a surgical procedure with more than five risk factors has a 40 to 80% chance of developing a VTE, and this is associated with a 0.2 to 5% rate of fatality from a PE.[2] According to the RAM shown in Table 41.3, the patient described in the case study presented with nine VTE risk factors totaling 22 points, which clearly placed him in the highest risk category (Table 41.4). Based on these data, the conservative approach of a month of anticoagulation therapy was chosen. Although there may be concerns over the expense, or the risk of bleeding or any other adverse event, this is a small concern compared with the ≤5% risk of a fatal event. Few passengers would board a plane knowing there to be up to a 5% risk of a fatal crash, begging the question, therefore, as to why an individual would choose not to use effective prophylaxis when there are no clinical data contraindicating such an approach.

Furthermore, often overlooked in this equation is the impact of postoperative thrombosis. Postoperative DVT can occur asymptomatically in the lower limbs, but if part of a clot breaks off, it may embolize to the right atrium. Right-to-left shunt may then occur through a patent foramen ovale that temporarily opens due to atrial dilation in response to the thrombus. Known as a *paradoxical embolism*, this allows the clot to pass into the systemic system, whereupon it may lodge in the brain and lead to nonhemorrhagic stroke. The patient then has a 50% chance of residual damage, including paralysis due to stroke, and 20% of patients may die. Is this a risk worth taking in the postoperative patient simply because they may be perceived to be at low risk? Finally, it is likely that while hospitalized and during the first week post-discharge, this patient will not be fully ambulatory. This immobilization is very difficult to quantify but provides additional impetus for prolonged prophylaxis. Thus, with a

total risk factor score of 22, it would seem wise to offer the case study patient a prophylactic approach at least equal to that shown effective for patients with fewer risk factors.

Accumulating Evidence Yet Absence of Guidelines

In situations for which specific data are not available, a conservative approach should be followed and physicians must use reason where level-1 evidence is lacking. For example, in terms of our case study patient, no clear guidelines exist to guide management. Yet looking at the literature, we see a strong case for a conservative approach. Two studies using the LMWHs dalteparin[56] and enoxaparin[46] have shown the efficacy of prolonging LMWH prophylaxis for a further three weeks in preventing DVT after major abdominal surgery in patients with cancer with no increase in bleeding complications.[57] An increased dose of the LMWH dalteparin from 2500 to 5000 IU once daily for seven days significantly reduced the incidence of VTE in cancer patients, with no increase in bleeding complications, a result of particular significance given that cancer patients are at increased risk for bleeding.[48] Long-term LMWH (dalteparin 200 IU/kg for 6 months) also has been shown to be more effective than an oral anticoagulant in reducing recurrent VTE in cancer patients with no increased risk for bleeding.[53] Further studies suggest benefits of LMWH for improved cancer survival.[52] This improved survival is thought to be associated with the anti-angiogenic properties of LMWH that inhibit tumor progression.[55]

The Importance of Weighting Risk Factors

Without accounting for all risk factors, inadequate prophylaxis may result. Although the aim is to develop a practicable RAM that overcomes the hindering complexities of its predecessors, this must not be at the expense of oversimplification. For instance, in its categorization of risk groups, the current ACCP guidelines lists patients >60 years undergoing surgery as a high-risk group with IPC as an acceptable sole means of prophylaxis.[2] Is this misleading when we note the increased incidence of VTE in cancer patients (up to 6 times higher in individuals with cancer than in those without a malignancy[47]) and see that LMWH or UFH are presented as the mainstays of prophylaxis in this group? By assigning six points to this patient (2 each for surgery, cancer, and age >60 years) as suggested in our RAM, the patient would clearly be placed in the highest risk group, underlining the importance of weighting the factors. Another key element was studied by Borow & Goldson (1981) where incidence of venographic DVT was found to be related to surgery duration (20% at 1–2 h, 46.7% 2–3 h, 62.5% > 3 h). In this same study, age was also stratified (40–60, 61–70, 61–70, >71 years), a weighting that is also employed in our RAM and further validates the weighted scoring system. We are currently in the process of implementing the RAM in the electronic record and adding a reminder to encourage prophylaxis. This aims to build upon the positive results (a 41% reduced risk of VTE at 90 days) shown with the electronic alert developed by Kucher et al. (2005) by combining this with a stratified approach to prophylaxis methods using weighted risk factors.[51]

SUMMARY

High-quality clinical data are unlikely to be available to guide thromboprophylactic decisions in all clinical situations, particularly for medical patients in whom VTE has been less extensively studied. Thorough and up-to-date academic guidelines are available and are the foundation for treatment regimens, but with new trial data constantly emerging, there will always be some disparity between the guidelines and clinical practice.

Despite the availability of effective methods of prophylaxis, both surgical and nonsurgical patients continue to be placed at risk of VTE and its potentially fatal complications, such as PE or stroke, due to the underuse of thromboprophylaxis. Prophylaxis is also being prescribed inappropriately, with patients at highest risk often receiving ineffective treatment due to misconceptions of VTE risk and concerns over the safety of anticoagulant therapy.

Where firm recommendations are available, the physician should treat according to the evidence, but where evidence is lacking, the physician should assess each patient based on their medical and clinical status and use a risk factor model to help stratify patients according to risk. Using this hybrid approach where necessary, which combines academic guidelines and intelligent clinical practice, more patients should receive appropriate prophylactic treatment tailored to their individual risk.

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C H A P T E R

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Venous Thromboembolism Prophylaxis in the General Surgical Patient

JOSEPH A. CAPRINI and J.I. ARCELUS

ABSTRACT

General surgery is associated with a significant risk of venous thromboembolism (VTE). The high prevalence and frequently silent onset of this condition underscore the importance of risk assessment and appropriate prophylactic measures. Individual risk assessment is critical for the selection of appropriate prophylactic methods for general surgical patients. Intermittent pneumatic compression and graduated compression stockings have been shown to reduce the risk for postoperative development of VTE in moderate-risk surgical patients. In very high-risk surgical patients, such as those with malignant disease, pharmacologic prophylaxis given for up to four weeks is necessary. Unfractionated heparin and low-molecular-weight heparins are safe and effective for VTE prophylaxis in this patient population. However, recent data from prospective registries show that most patients who develop postoperative symptomatic VTE had received some form of prophylaxis, which was obviously ineffective.[1] Therefore, more effective methods are necessary for very high-risk patients. A novel selective factor Xa inhibitor, fondaparinux, also has been shown to be safe and effective for VTE prophylaxis in patients who have undergone abdominal surgery, especially in patients with cancer. These results suggest that fondaparinux may further improve VTE prevention in the general surgical population. No method of VTE prophylaxis is appropriate for every patient; therefore, the benefits and risks of each method of VTE prophylaxis should be weighed for the individual patient so that the optimal prophylactic regimen can be initiated.

INTRODUCTION

Patients undergoing major surgery are at an up to 20-fold increased risk for development of venous thromboembolism (VTE), an often asymptomatic condition that encompasses both deep vein thrombosis (DVT) and pulmonary embolism (PE).[2] Kakkar and colleagues demonstrated in 1975 that the observed rate of DVT in general surgical patients who did not receive VTE prophylaxis was nearly 30%.[3] A meta-analysis of randomized trials in general, orthopedic, and urologic surgery, conducted prior to 1988, reported similar results (27% incidence of DVT and 3.4% incidence of fatal PE).[4] Pooled data from more than 50 trials published between 1970 and 1985 show that the overall postoperative incidence of DVT as assessed by fibrinogen uptake test (FUT), a nuclear study in which radiolabeled fibrin is incorporated into newly formed thrombi, and/or venogram ranges from 19 to 29% in untreated patients who undergo general surgery. The rate of PE in these studies was approximately 1.6%, and the rate of fatal PE was 0.9%. The majority of patients included in this pooled analysis underwent elective gastrointestinal surgery; some study populations also included patients who had undergone gynecologic, thoracic, urologic, or vascular surgery.

In the United States, DVT is reported to affect up to 145 individuals per 100,000 individuals per year in the general population, and it is accompanied by PE in up to 69 individuals per 100,000.[5] Approximately 14 to 16% of all symptomatic VTE diagnosed in the western world is diagnosed in postoperative patients and almost half of them are general surgical patients.[1] Because of the strong data demonstrating

the high risk of VTE in general surgical patients, clinical studies without prophylaxis are no longer performed in this patient population, and thus, the current risk of VTE in unprotected patients is unknown. The incidence of VTE in this patient population without prophylaxis was approximately 30% in studies done in the mid- to late 1970s using very sensitive objective diagnostic methods.[4,6] With pharmacologic prophylaxis, the incidence ranges from 4.6 to 8%. Despite the seriousness of the condition and its prevalence, it has been demonstrated that 25 to 62% of general surgical patients do not receive any form of prophylaxis.[7,8] On the other hand, recent data reveal that more than 50% of patients developing postoperative VTE had received pharmacologic prophylaxis.[1,9] Clearly, there is a need to improve VTE prevention in general surgical patients.

VTE is difficult to diagnose because it is often asymptomatic, and, when present, symptoms are nonspecific. Symptoms of DVT include leg pain, heaviness, and swelling. Symptoms of PE include chest pain, shortness of breath, tachypnea, fever, transient orthostatic hypotension, fainting spells, sudden death, and postoperative stroke. Although many surgeons may think that postoperative VTE is uncommon, many most likely see the signs of VTE often, but overlook their possible connection to VTE. In 70 to 80% of patients who die from PE in the hospital, this diagnosis was not even considered prior to the patient's death.[10,11]

The prevention of VTE is important because both symptomatic and asymptomatic VTE are associated with long-term consequences, even when the condition is diagnosed and treated. A common serious complication associated with DVT is post-thrombotic syndrome (PTS), which is characterized by permanent vein damage that results in chronic leg swelling that worsens during the day and may be accompanied by the presence of varicose veins, edema, skin discoloration, and skin ulcerations.[12,13] In a prospective study of 528 patients with venography-confirmed DVT, 19% of whom were postoperative, the cumulative incidence of PTS at two, five, and eight years following initial diagnosis and treatment was 24.5%, 29.6%, and 29.8%, respectively.[13] PTS also represents a significant economic impact of DVT. It has been estimated that 15 million Americans are afflicted with PTS and that two million work days are missed annually due to the condition.[14]

Recurrent DVT or PE is also a common clinical consequence of VTE. The cumulative incidence of recurrent VTE after two, five, and eight years of follow-up was 17.2%, 24.3%, and 29.7%, respectively.[13] A rare, but serious consequence that is associated with both symptomatic and asymptomatic DVT is fatal PE. It has been estimated that less than 50% of patients are alive one year following an acute PE.[15] In addition, almost 1% of patients who survive an acute PE will develop chronic pulmonary hypertension.[16] PE also is associated with embolic stroke in patients with patent foramen ovale (PFO), a condition estimated to be present in 10% to nearly 30% of the general population.[17–20] PE can lead to elevated pressures in the right side of the heart, which can lead to expansion of PFO. A clot or part of a clot can move from the right chamber to the left chamber of the heart through the expanded PFO, causing cerebral and peripheral ischemic events characteristic of paradoxical embolism (passage of a clot from a vein to an artery).[21] These serious, disabling, and sometimes fatal consequences of VTE underscore the importance of prevention in patients at risk, including patients undergoing general surgery.

Although a high incidence of VTE has been demonstrated in general surgical patients, risk for VTE varies among general surgery patients, and different methods of prophylaxis are appropriate for different levels of risk. An optimal approach to risk assessment and VTE prophylaxis should combine evidence-based, consensus, and clinical practice guidelines with clinical experience where a lack of science exists. Several risk factor assessment models have been proposed to predict risk.[22–29]

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Although the risk for VTE is increased in all patients undergoing general surgery, the relative risk for postoperative development of this complication varies among individual patients based on several factors, including the length of immobilization following surgery, the type of surgery performed, and the presence of comorbid conditions (see Table 42.1).[2,15,30–33] Important patient-specific risk factors for VTE include age (older than 40 years), ethnicity, and body mass index greater than 25.[5,30,32,34–36] A recent retrospective study in general surgical patients found that, although a steady rise in the incidence of VTE is seen between 40 and 75 years of age, this increase does not continue above the age of 75 years.[30]

Immobilization for an extended period of time is a well-established risk factor for VTE, and early mobilization following surgery has been shown to lower the risk for postoperative VTE.[32,33] There is also strong evidence that the type of surgical procedure that a patient undergoes is predictive of the risk for postoperative VTE.[30] Major general surgery (usually defined as abdominal or thoracic operations that require general anesthesia lasting ≥45 minutes) is associated with a high risk of VTE. Orthopedic surgery also is associated with an even higher risk for VTE. In a retrospective study of more than one million surgical patients, the incidence of symptomatic VTE was highest among patients who underwent orthopedic surgery of the hip or knee as well as those who had invasive neurosurgery involving brain incision, excision, or biopsy.[30] Other procedures associated with a substantially increased risk for VTE included major vascular surgery, small- or large-bowel resection, gastric

TABLE 42.1 Risk Factors for VTE[15,33]

Patient factors	
• Age >40 years	• Pregnancy
• Prolonged immobility	• Puerperium
• Obesity	• High dose estrogen therapy
• History of DVT or PE	• Varicose veins
Medical/surgical risk factors	
• Major surgery (especially involving the abdomen, pelvis, lower extremities)	• Acute respiratory failure
• Malignancy (especially pelvic, abdominal, metastatic)	• Congestive heart failure
• Myocardial infarction	• Inflammatory bowel disease
• Stroke	• Nephrotic syndrome
• Fractures of the pelvis, hip, or leg	• Pacemaker wires
• Polycythemia	• Paraproteinemia
• Paroxysmal nocturnal hemoglobinuria	• Behcet's syndrome
Hypercoagulable states	
• Lupus anticoagulant and antiphospholipid antibodies	• Disorders of plasminogen and plasminogen activation
• Homocysteinemia	• HIT
• Dysfibrinogenemia	• Protein C deficiency
• Myeloproliferative disorders	• Protein S deficiency
• Antithrombin deficiency	• Hyperviscosity syndromes
• Factor V Leiden	• Prothrombin gene mutation 20210A
• Disseminated intravascular coagulation	

bypass, radical cystectomy, kidney transplantation, and below-the-knee amputation.[30] A lower risk of VTE was reported with radical neck dissection, inguinal hernia repair, appendectomy, laparoscopic cholecystectomy, transurethral prostatectomy, repair of a cystocele or rectocele, cruciate ligament repair, and thyroid or parathyroid surgery.[30]

Certain medical conditions, including congestive heart failure, chronic obstructive pulmonary disease, recent myocardial infarction, stroke, nephrotic syndrome, inflammatory bowel disorder, and systemic lupus erythematosus are known to increase the risk for VTE.[15,33] There is a particularly strong association between cancer and VTE.[35,37] Cancer patients undergoing surgery have a two- to five-fold increased risk for postoperative VTE, compared with noncancer patients undergoing the same procedures.[37,38] In addition, among patients with DVT, those with cancer have a more than two-fold increased risk for VTE recurrence than those without cancer.[37] In a retrospective study of 986 patients who underwent venous ultrasonography because of suspected DVT, 12% of patients with confirmed DVT were subsequently found to have cancer.[39] Conversely, it has been shown that clinically apparent VTE is present in as many as 15% of all cancer patients, with much higher incidences reported in postmortem studies.[40,41] The likelihood for the development of VTE in cancer patients is increased among those with more advanced clinical disease and varies by tumor type.[42,43] Malignancies stemming from the uterus, brain, ovary, pancreas, stomach, kidneys, and colon are among those that have been associated with the highest relative risk for VTE.[42]

TABLE 42.2 Categories of Risk for VTE in Patients Undergoing General Surgery and Recommended Prophylactic Regimens[99]

Low risk (1 factor)	Moderate risk (2 factors)	High risk (3–4 factors)	Highest risk (≥5 factors)
Early ambulation	GCS or IPC	LDUH (5,000 U BID) or LMWH (≤3400 U QD) or fondaparinux (2.5 mg QD)	GCS or IPC and LDUH (5,000 U TID), LMWH (>3,400 U QD), or fondaparinux (2.5 mg QD)

Acquired or inherited thrombophilia disorders can also increase risk of VTE. A mutation in the factor V gene resulting in resistance to the action of protein C, known as factor V Leiden, is the most common cause of familial thrombophilia.[44] This mutation can increase the risk of VTE to 50- to 80-fold that of the general population in individuals who are homozygous for the mutation and to three-fold in heterozygous individuals.[44,45] The second most common cause of familial thrombophilia is the prothrombin 20210A mutation. This mutation is associated with a three-fold increase in the risk for VTE. Another thrombophilia disorder is antiphospholipid antibody syndrome. Thromboembolic events are reported in approximately one-third of antiphospholipid-positive patients. The risk of recurrent thrombosis in these patients ranges from 22 to 69%.[46] Other thrombophilia disorders include hyperhomocysteinemia; protein C, protein S, and antithrombin deficiencies; and elevated levels of coagulation factors, including factors II, VIII, IX, and XI. Detection of these disorders is critical for identification of a patient's true risk for VTE and should be a factor in a patient's decision of whether or not to undergo elective surgery.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Aside from aggressive mobilization, the American College of Chest Physicians does not recommend specific measures for patients at low risk for VTE (risk factor score of 0 to 1; see Table 42.2). Pharmacologic therapies (unfractionated heparin [UFH, 5000 U bid] or low-molecular-weight

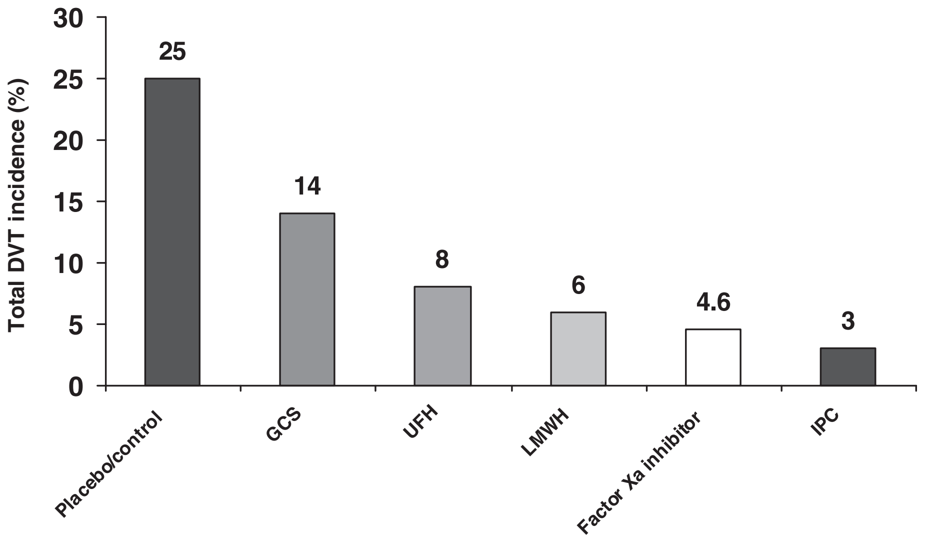


FIGURE 42.1 Incidence of VTE with currently available prophylactic methods following general surgery.*

*All incidences are for DVT after general surgery based on meta-analyses from Geerts 2001 except the incidence for Factor Xa inhibitor, which includes venographically proven DVT, symptomatic DVT, and PE and is based on the results from PEGASUS.[94]

heparin [LMWH, <3400 U QD]) and nonpharmacologic interventions are recommended for the prevention of VTE in patients at moderate risk (risk factor score of 2). For patients at high risk (risk factor score of 3–4), pharmacologic therapies (UFH [5000 U TID] or LMWH [>3400 U QD]) and intermittent pneumatic compression (IPC) are recommended for protection against VTE. For patients at highest risk for VTE (risk factor score ≥5), pharmacologic therapy using high-risk doses always is recommended in the absence of contraindications, and the adjunctive use of mechanical prophylaxis also is recommended.

Nonpharmacologic Interventions for the Prevention of Venous Thromboembolism

Nonpharmacologic VTE prevention strategies often are appealing because they do not increase the risk for bleeding; however, they have not been as extensively studied as pharmacologic prophylaxis.[47] It is recommended that early and "aggressive" ambulation be a routine part of postoperative care in all patients unless there is an absolute contraindication. Although early mobilization following surgery has been shown to significantly lower the risk for postoperative VTE,[32] it is recommended as the sole method of prophylaxis only for low-risk patients, those younger than 40 years of age without any additional risk factors for VTE who are undergoing minor surgery (outpatient surgery lasting less than 45 minutes). For surgical patients at moderate risk for VTE (major surgery with 2 additional risk factors), mechanical methods of prophylaxis, including graduated compression stockings (GCS) and IPC, have been very safe and effective modalities and have been very well accepted in the United States, particularly in patients at high risk for bleeding complications.

The results of several meta-analyses suggest that IPC can reduce the risk of DVT in general surgical patients; however, these meta-analyses included a small number of small clinical trials.[47–49] The incidence of DVT in general surgical patients who received IPC was 3% (95% CI, 1% to 8%) in one recent meta-analysis of two studies (see Figure 42.1), a result similar to that observed in previous meta-analyses.[47–49] Several head-to-head clinical trials have shown that IPC has similar efficacy to low-dose UFH and LMWH for the prevention of DVT in general surgery patients.[50–53] Although there is strong evidence supporting the use of IPC alone in moderate-risk patients, it has not been studied as thoroughly as pharmacologic agents and is recommended only as an adjunctive therapy in surgical patients at high and highest risk for VTE (see Table 42.2).

Elastic stockings also have been shown in meta-analyses to substantially reduce the incidence of lower extremity DVT in patients who have undergone general surgery.[54] A recent systematic review conducted by the Cochrane Collaboration analyzed seven randomized controlled trials in surgical patients (4 general surgery [abdominal/pelvic/thoracic], 1 gynecologic surgery, 1 neurosurgery, 1 orthopaedic surgery). The incidence of lower-limb DVT in patients who used elastic stockings was significantly reduced, compared with those who did not use this intervention (15% vs 29%, $P < .00001$).[55] The incidence of DVT following general surgery was 14% (95% CI, 10% to 20%) with GCS in a meta-analysis of three studies. In another meta-analysis of

11 studies that investigated the prophylactic efficacy of GCS in patients who had undergone moderate-risk surgery (9 abdominal surgery, 1 gynecologic surgery, and 1 neurosurgery), elastic stockings reduced the risk for lower-limb DVT by 68%.[54] The current evidence suggests that GCS is effective in moderate-risk general surgical patients, but there are few data exploring the efficacy of this intervention in high-risk general surgical patients or surgical patients with cancer. Limitations of GCS include a lack of standardization of stockings, difficulty fitting patients of unusual size or shape, and poor compliance.

Clinical trials have shown that combining GCS or IPC with pharmacologic prophylaxis, such as heparin, results in better protection against VTE than either of these approaches used alone.[55,56] The incidence of DVT was only 1.5% in a group of 328 surgical patients who received a pharmacologic and antistasis agent, compared with 26.8% in a control group who did not receive prophylaxis.[57] In a study in cardiac patients (N = 2551) randomized to receive subcutaneous heparin alone or in combination with IPC, the incidence of PE was 62% lower (1.5% vs 4%) in those who received combination therapy ($P < .001$).[58] In 249 patients who had suffered a stroke, combined modality therapy resulted in a reduction of DVT (0.23% vs 9.2%) and PE (0% vs 2.4%).[59] These findings suggest that although mechanical prophylaxis may not be appropriate as a sole intervention in patients at high risk for VTE, it may offer additional protection in patients receiving pharmacologic therapy.

Further support for the benefit of combined mechanical and pharmacologic prophylaxis for the prevention of VTE came from the APOLLO study. In this double-blind, placebo-controlled trial, patients undergoing major abdominal surgery (N = 1309) received IPC with or without the Factor Xa inhibitor fondaparinux.[60] Combined IPC and fondaparinux therapy produced a significant reduction in the incidence of all VTE from 5.3% (IPC alone) to 1.7% ($P = .004$). The rates of proximal DVT were also significantly reduced in the combined therapy group from 1.7% (IPC alone) to 0.2% ($P = .037$). Patients who received fondaparinux treatment had significantly more major bleeding episodes than those who received IPC alone (1.6% vs 0.2%, $P = .006$); however, none of these bleeds was fatal or involved critical organs. In addition, a major bleeding rate of 1.6% is comparable to the major bleeding rates observed with abdominal surgery (colorectal surgery) with enoxaparin and UFH.[61] Although patients might be at a higher risk for bleeding with the addition of pharmacologic anticoagulation treatments, combined therapy has been shown to be significantly more effective for the prevention of VTE following major surgery than mechanical prophylaxis alone.

Inferior vena caval (IVC) filters are not routinely used for the prevention of DVT, but rather for the prevention of PE in patients who either fail or have contraindications to other prophylactic therapies, particularly anticoagulants.[62] Prophylactic use of IVC filters is indicated for patients with established VTE with an absolute contraindication to anticoagulation, serious complication while on anticoagulation (i.e., hemorrhage, thrombocytopenia, or drug reaction), or documented failure on anticoagulation.[62] In addition, IVC filters can be effective in patients with pelvic fractures or closed head injuries who are at high risk for thrombosis or have had a previous thrombosis.

IVC filters are generally safe and have been shown to reduce the incidence of PE and fatal PE to 2.6 to 3.8% and 0.3 to 1.9%, respectively, in patients at risk for VTE.[63] An increase in recurrent DVT has been observed with IVC filters. Decousus and colleagues demonstrated a reduction in symptomatic and asymptomatic PE at 12 days, from 4.8 to 1.1% in patients with DVT who received filters, but at two years the incidence of recurrent DVT was significantly increased in these patients (20.8% vs 11.6%, $P = .02$).[64] However, eight-year follow-up on these patients was recently reported, and although the significant reduction in the incidence of PE was maintained ($P = .01$), at eight years there were no significant differences in recurrent DVT ($P = .08$), PTS, or overall mortality with and without filters.[65] Several types of IVC filters are available, but the Greenfield filter is the only filter with good long-term follow-up.[66,67] Although relatively rare, other complications associated with IVC filter placement and long-term use include migration of the filter, postfilter caval thrombosis, and PTS.[63,68]

In summary, nonpharmacologic prophylaxis can be very effective in reducing the incidence of DVT in general surgical patients at moderate risk for VTE (see Table 42.2). However, they have not been as extensively studied as pharmacologic agents and are not recommended as the sole method of prophylaxis in patients at higher risk for VTE. However, in conjunction with pharmacologic agents, mechanical prophylaxis can be very effective in reducing the incidence of VTE in these patients. On the other hand, mechanical prophylaxis with stockings or IPC is recommended in patients with a high risk for bleeding.

Pharmacologic Methods for the Prevention of Venous Thromboembolism

Commonly used pharmacologic therapies for prevention of VTE in patients undergoing general surgery include subcutaneous UFH and LMWH (enoxaparin, dalteparin, nadroparin, or tinzaparin). Low-dose subcutaneous UFH was the first pharmacologic agent to be widely investigated for prevention of VTE in patients undergoing general surgery. In the early 1970s, Kakkar and colleagues demonstrated that this therapy significantly reduced the risk for both DVT and PE in this patient population.[6,69] Low-dose UFH is highly effective therapy for the prevention of VTE in patients undergoing general surgery, including those with underlying malignancy.[6,47,69] In a landmark prospective randomized

study of 4121 patients undergoing major surgery (primarily abdominal, gynecologic, or urologic surgery), UFH prophylaxis reduced the incidence of DVT from 25% to 8% ($P < .005$).[6] Patients treated with UFH also had a significantly reduced incidence of PE ($P < .005$) and death from PE ($P < .005$) compared with control patients.[6]

A meta-analysis of 46 trials by Collins and colleagues that included 16,000 patients who had undergone general, orthopedic, or urologic surgery confirmed Kakkar's results, with a DVT incidence of 27% without prophylaxis compared with 10.6% with UFH and a fatal PE incidence of 3.4% and 1.7%, respectively.[4] The incidence of DVT was 8% (95% CI, 7% to 8%) with UFH following general surgery in a recent meta-analysis of 47 clinical studies. It has been suggested that the administration of 5000 U of UFH TID is more effective than 5000 U BID, without increased bleeding,[4,47] but no direct comparison studies have been conducted. In general, UFH can be given twice daily in moderate- to high-risk patients but should be given three times daily in higher-risk patients.

Although UFH is effective for the prevention of DVT and PE in general surgical patients, bleeding complications associated with this therapy present a serious safety concern.[4,6,47] Cancer patients may be at higher risk for hemorrhagic complications with UFH than noncancer patients.[70] Another limitation of UFH is its association with heparin-induced thrombocytopenia (HIT).[72] UFH has been associated with up to a 5% incidence of HIT, an antibody-mediated process characterized by a dramatic drop in platelets.[71] In 20% of cases, HIT develops into thrombosis. UFH can also cause osteopenia by binding to osteoblasts, which stimulates osteoclast activation and results in bone breakdown when used long term. The short half-life of UFH (0.5 to 2 hours) relative to other anticoagulants is another limitation of UFH because it necessitates more frequent dosing; however, the short half-life can also be an advantage in the case of bleeding complications or renal failure. Another advantage of UFH is that an antidote, protamine sulfate, is available for situations when immediate reversal is required, although reversal is not without risks.

LMWHs appear to be at least as effective as UFH for the prevention of DVT in clinical trials of patients undergoing general surgery (see Figure 42.1).[89] Overall, the residual incidence of VTE in abdominal surgery patients receiving LMWH ranges from about 5 to 15%, with the highest rates in patients with cancer.[76,77] The incidence of DVT with LMWHs following general surgery was 6% (95% CI, 6% to 7%) in a recent meta-analysis of 21 clinical studies. Available LMWHs appear to be similarly effective for the prevention of VTE. Both enoxaparin and dalteparin have been shown to reduce the incidence of DVT in patients undergoing general surgery to rates of approximately 6 to 8%; however, direct comparison studies have not been conducted.[75,78]

LMWHs appear to be effective in VTE prophylaxis, even in patients with cancer.[76,77,79,80] The incidence of VTE in patients with cancer who were given enoxaparin was slightly lower than that observed in patients given UFH (14.7% vs 18.2%) in a study of patients undergoing abdominal surgery for malignant disease (N = 1115).[76] In addition, when patients undergoing planned curative surgery for abdominal or pelvic cancer were given LMWH for six to 10 days and then randomized to receive extended prophylaxis with LMWH or placebo for 21 days, the incidence of venographically demonstrated VTE at three months was significantly reduced (5.5% vs 13.8%, $P = .01$) with extended prophylaxis.[77] There was no significant increase in bleeding with extended prophylaxis. These results suggest that LMWH is at least as effective as UFH in general surgical patients with cancer and that extended prophylaxis with LMWH is safe and can significantly reduce the incidence of VTE in general surgical patients with cancer.

It has been suggested that survival may be increased in patients with cancer who receive LMWH compared with UFH, although the reason for this is not clear. In women with previously untreated breast and pelvic cancer who had undergone primary surgery, those who received LMWH (n = 160) had significantly better long-term survival at 650 days than those who received UFH (n = 164, $P = .0066$).[81] A significant survival benefit (12.6% vs 27%, $P = .041$) also was observed with LMWH in a subset of patients with cancer who were treated for DVT with a LMWH or UFH.[82,83] In a randomized controlled study where patients with advanced cancer (N = 385) were randomized to receive an LMWH once-daily for one year or placebo, there was no significant difference in survival at one, two, or three years; however, in a subset of patients with a better prognosis, survival was significantly ($P = .03$) improved at two and three years (78% vs 55% and 60% vs 36%, respectively).[84] These results suggest that there may be some survival benefit of LMWH in patients with cancer, particularly those at early stages of malignancy.

Although there is some evidence that LMWH therapy may lead to fewer bleeding complications than observed with UFH, results from clinical studies have been inconsistent, and bleeding remains an important safety concern associated with LMWH, particularly when it is used at higher doses.[73–76,85–87] Advantages of LMWHs over UFH include a higher anti-Xa activity compared with antithrombin activity, better bioavailability at low doses, no monitoring required, and a longer half-life (4 hours vs 0.5 to 2 hours), allowing for once-daily dosing in some patients. However, a long half-life can sometimes be a disadvantage in the case of bleeding complications. In addition, LMWHs are incompletely reversed by protamine sulfate.[88] Other disadvantages of LMWHs include renal excretion, precluding use in patients with severe renal failure, and increased cost relative to UFH. Furthermore, LMWHs also carry a risk for HIT and

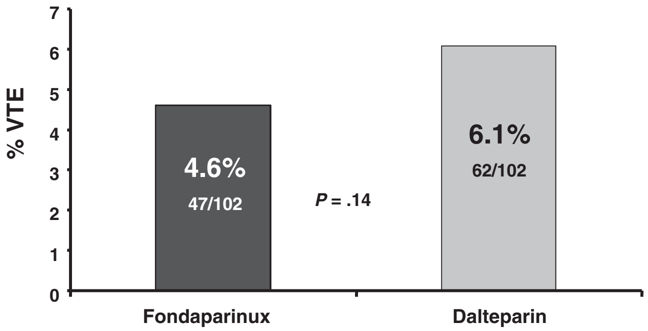


FIGURE 42.2 VTE reduction with fondaparinux versus dalteparin in high-risk abdominal surgical patients.[94]

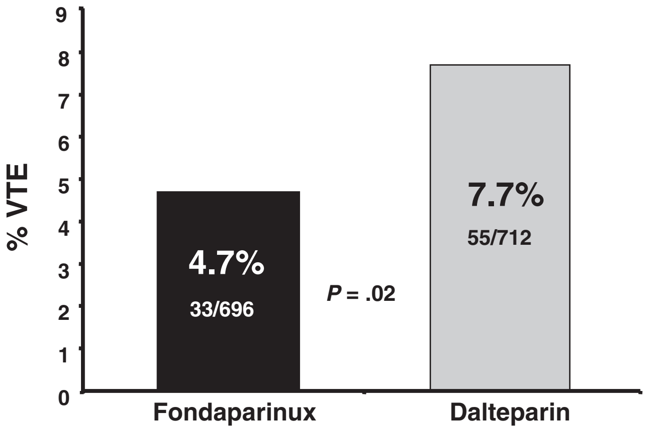


FIGURE 42.3 VTE reduction with fondaparinux versus dalteparin in high-risk abdominal surgical patients with cancer.[94]

should not be used in patients at risk for or with established HIT, although they appear to be associated with a lower incidence than UFH.

Fondaparinux is the first in a new class of antithrombotics known as factor Xa inhibitors, which are characterized by targeted inhibition of coagulation. Fondaparinux is a novel synthetic pentasaccharide that selectively binds to antithrombin III with enhanced neutralization of factor Xa.[90] It has demonstrated greater efficacy than LMWH in VTE prophylaxis following total joint replacement[91,92] and hip fracture surgery[93] and has been evaluated for VTE prophylaxis in patients undergoing general surgery. In the Pentasaccharide in General Surgery Study (PEGASUS), the efficacy and safety of postoperative fondaparinux (2.5 mg once daily) was compared with that of the LMWH dalteparin started preoperatively in high-risk abdominal surgical patients.[94] This multicenter, randomized, double-blind study included 2900 high-risk abdominal surgical patients, in which high risk was defined as patients older than 60 years of age or older than 40 years of age with one or more risk factors including cancer, obesity (BMI >30 for men and >28.6 for women), history of VTE, heart failure (NYHA grade III or IV), chronic obstructive pulmonary disease, or inflammatory bowel disease.[94]

PEGASUS showed that the rates of VTE (venographically proven DVT, symptomatic DVT, or fatal or nonfatal PE) up to day 10 among patients treated with fondaparinux and dalteparin were 4.6% and 6.1% ($P = .14$), respectively, representing a 24.5% reduction in the incidence of VTE in favor of fondaparinux (see Figure 42.2).[94] At postoperative day 32, symptomatic DVT was seen in 0.8% of patients treated with fondaparinux and in 1.0% of patients who received dalteparin.[94] The difference in the incidence of major bleeding between the two treatment groups was not significant (3.4% fondaparinux vs 2.4% dalteparin, $P = .12$).[94] These results demonstrate that fondaparinux is at least as effective, if not more, than UFH and LMWH in preventing VTE in general surgical patients (see Figure 42.1). Based on this data, fondaparinux was recently approved in the United States for VTE prevention in abdominal surgical patients undergoing general anesthesia for longer than 45 minutes who are older than 40 years of age and have one of the following risk factors: neoplastic disease, obesity, chronic obstructive pulmonary disease, inflammatory bowel disease, history of DVT or PE, or congestive heart failure. In addition, it is indicated for abdominal surgical patients undergoing general anesthesia lasting longer than 45 minutes who are older than 60 years of age with or without one or more of the risk factors just listed.

A post-hoc analysis was performed to compare the effects of the two therapies in the 68% of the evaluable study population who underwent surgery for cancer.[94] In the cancer subpopulation, fondaparinux significantly reduced the incidence of VTE compared with dalteparin from 7.7 to 4.7% ($P = .02$), representing a 39% reduction in the incidence of VTE (see Figure 42.3). The incidence of major bleeding was similar between groups (3.4% fondaparinux vs 2.5% dalteparin). These preliminary findings suggest that postoperative fondaparinux is at least as effective and safe as preoperative dalteparin for the prevention of VTE after abdominal surgery and is significantly more effective than dalteparin in cancer patients undergoing the same procedures.

Another advantage of fondaparinux is that, unlike UFH and LMWH, it has not been associated with HIT. Because the fondaparinux molecule does not bind to platelet factor 4, it cannot form the complex that reacts with the platelet-activating antibody, and it does not cross-react with HIT antibodies from patients with confirmed type II HIT.[95,96] Fondaparinux has also been shown to be safe for extended prophylaxis (4 weeks),[97] although this was shown in patients who had undergone hip fracture surgery, not in general surgical patients. In addition, because fondaparinux does not interfere with thrombin binding, it has no negative effect on wound healing. Further, fondaparinux has a 17-hour half-life, which allows for once-daily dosing, and there is no dose alteration required in patients weighing less than 50 kg or

renally impaired patients. However, no antidote is available and a long half-life also can be a disadvantage in the case of bleeding complications. Fondaparinux is renally excreted and should not be used in patients with kidney failure and should be avoided in patients undergoing neuraxial anesthesia, as there is the potential for epidural hematoma formation.

There are a variety of agents available for the prevention of VTE in patients undergoing general surgery. No single agent is optimal for all patients. Different agents should be used in patients at different levels of risk and patient characteristics and comorbid conditions can make one agent more appropriate than another in a certain patient. The stratification of general surgery patients by risk for VTE can guide surgeons in their selection of appropriate VTE prophylaxis.

RISK STRATIFICATION

The risk for VTE ranges from low to very high in patients undergoing general surgery. Risk category placement is dependent upon the presence of factors that influence the risk for VTE, including type of surgery, age, immobilization, and comorbidities. It has been demonstrated that up to 36% of general surgical patients had three or more risk factors, placing them in the high or highest risk groups.[98] These are groups in which pharmacologic VTE prophylaxis is strongly recommended. The number of factors that can influence the risk of VTE and the variety of agents available for VTE prophylaxis can make risk assessment and management difficult.

Risk stratification has been suggested as a means of determining the risk for VTE in patients undergoing surgery and of guiding the selection of appropriate prophylactic measures. Risk assessment models, like the one pictured in Figure 42.4, can be used to assign each patient a total risk factor score, which can then be used to categorize patients into one of four risk categories (low, moderate, high, and highest) (see Table 42.2).[99] An appropriate method of VTE prophylaxis can be chosen based on the patient's level of risk, taking into consideration any contraindications to prophylaxis that may be present.

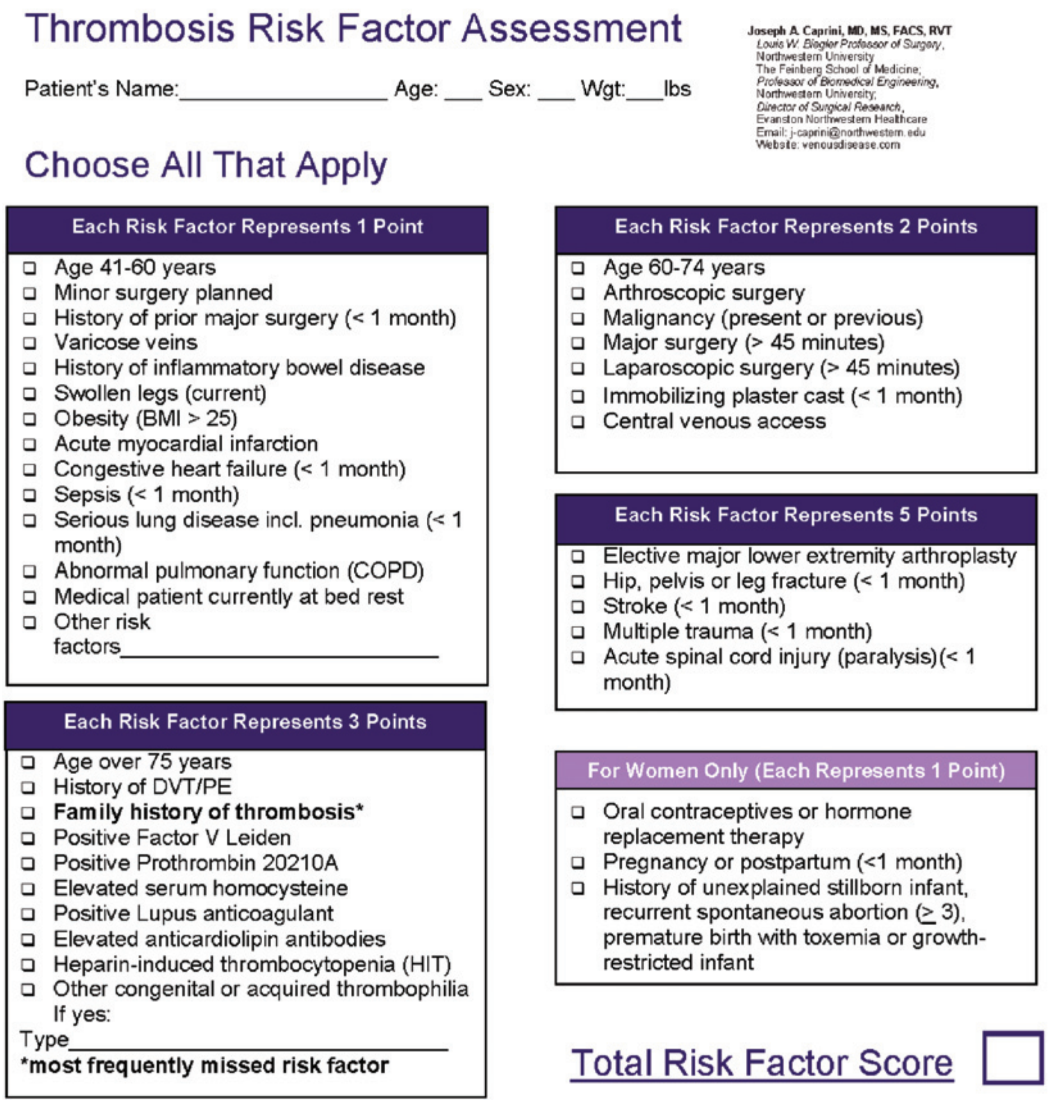
The incidence of VTE in patients in the low-risk category (1 risk factor) is so low already (approximately 2%),[14] that prophylactic measures would most likely not further reduce the risk. Thus, no measures above early ambulation are recommended in this patient population (see Table 42.2). The incidence of VTE ranges from 10 to 80% in the remaining groups;[14] therefore, prophylactic measures are recommended in these groups. Elastic stockings and IPC reduce the incidence of DVT to 14% and 3% (see Figure 42.1), respectively, and can be used alone in moderate-risk patients (2 risk factors). Although IPC has been shown to reduce the incidence of DVT to 3% following general surgery, it has not been extensively studied in general surgery and is not recommended as the sole method of prophylaxis in patients at greater than moderate risk for VTE.

Pharmacologic measures have been shown to produce lower incidences of DVT than mechanical methods of prophylaxis (see Figure 42.1) and therefore are recommended in patients at high and highest risk for VTE (see Table 42.2). Subcutaneous UFH (5000 U BID), LMWH (≤3400 U QD), or fondaparinux (2.5 mg QD) can be used in patients at high risk for VTE (3 to 4 risk factors). In patients at the highest risk for VTE (≥5 risk factors) higher doses of both subcutaneous UFH (5000 U TID) and LMWH (>3400 U QD) or fondaparinux (2.5 mg) should be used. Although fondaparinux has not been as extensively studied as UFH or LMWHs in general surgical patients, the results of PEGASUS (a 4.6% incidence of VTE)[94] suggest that fondaparinux is effective for VTE prophylaxis in this patient population and may be particularly effective in patients in the highest-risk category. In addition, for patients at highest risk for VTE, mechanical prophylaxis combined with pharmacologic prophylaxis can be more effective than pharmacologic prophylaxis alone. The recent APOLLO trial results emphasize the value of combined prophylaxis because, in that trial, the incidence of venographically positive DVT was 1.7% in moderate- and high-risk general surgical patients.[60]

As an alternative to a risk assessment model, it has been suggested that appropriate thromboprophylactic measures be used in all but very low-risk general surgical patients. At a minimum, it has been suggested that the use of elastic stockings, sequential compression devices, and LMWHs should be considered in all patients undergoing cancer surgery, a group considered to be at high risk for VTE. In a recent editorial comment, Goldhaber suggests using pharmacologic methods of prophylaxis for all hospitalized patients, according to easily implemented protocols. For those patients with contraindications to pharmacologic prophylaxis, mechanical methods should be used. Patients at very high risk for VTE should receive a combination of both pharmacologic and mechanical measures.[100]

CONCLUSION

Although the development of VTE is relatively common in the postoperative setting and is a frequent cause of sudden postoperative death, VTE prophylaxis remains underutilized. Because VTE is often asymptomatic and, when present, symptoms are nonspecific, surgeons may feel that they do not often see VTE in their practice. However, signs of VTE include leg pain, leg swelling, chest pain, shortness of breath, transient orthostatic hypotension, narcotic excess, fainting spells, hypoxia, sudden death, postoperative stroke, suspected myocardial infarction, and postoperative


Thrombosis Risk Factor Assessment

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Patient's Name:________________ Age: ___ Sex: ___ Wgt:___lbs

Choose All That Apply

Each Risk Factor Represents 1 Point

- ❑ Age 41-60 years
- ❑ Minor surgery planned
- ❑ History of prior major surgery (< 1 month)
- ❑ Varicose veins
- ❑ History of inflammatory bowel disease
- ❑ Swollen legs (current)
- ❑ Obesity (BMI > 25)
- ❑ Acute myocardial infarction
- ❑ Congestive heart failure (< 1 month)
- ❑ Sepsis (< 1 month)
- ❑ Serious lung disease incl. pneumonia (< 1 month)
- ❑ Abnormal pulmonary function (COPD)
- ❑ Medical patient currently at bed rest
- ❑ Other risk factors________________________

Each Risk Factor Represents 2 Points

- ❑ Age 60-74 years
- ❑ Arthroscopic surgery
- ❑ Malignancy (present or previous)
- ❑ Major surgery (> 45 minutes)
- ❑ Laparoscopic surgery (> 45 minutes)
- ❑ Immobilizing plaster cast (< 1 month)
- ❑ Central venous access

Each Risk Factor Represents 5 Points

- ❑ Elective major lower extremity arthroplasty
- ❑ Hip, pelvis or leg fracture (< 1 month)
- ❑ Stroke (< 1 month)
- ❑ Multiple trauma (< 1 month)
- ❑ Acute spinal cord injury (paralysis)(< 1 month)

Each Risk Factor Represents 3 Points

- ❑ Age over 75 years
- ❑ History of DVT/PE
- ❑ **Family history of thrombosis***
- ❑ Positive Factor V Leiden
- ❑ Positive Prothrombin 20210A
- ❑ Elevated serum homocysteine
- ❑ Positive Lupus anticoagulant
- ❑ Elevated anticardiolipin antibodies
- ❑ Heparin-induced thrombocytopenia (HIT)
- ❑ Other congenital or acquired thrombophilia If yes:

Type______________________________

***most frequently missed risk factor**

For Women Only (Each Represents 1 Point)

- ❑ Oral contraceptives or hormone replacement therapy
- ❑ Pregnancy or postpartum (<1 month)
- ❑ History of unexplained stillborn infant, recurrent spontaneous abortion (≥ 3), premature birth with toxemia or growth-restricted infant

Total Risk Factor Score ☐

FIGURE 42.4 Thrombosis risk factor assessment scoring sheet.

pneumonia, and most surgeons would agree that many of these conditions are relatively common following surgery.

Due to the significant morbidity and mortality that is associated with VTE, the risk of VTE must be considered in all general surgical patients. In this population, nearly 40% of patients are at high or highest risk for VTE (≥3 risk factors) and, therefore, require pharmacologic VTE prophylaxis. Risk stratification schemes may help to guide the intensity of clot-preventing measures. Risk stratification schemes like the one in Figure 42.4 may be helpful for assessing VTE risk in general surgical patients. Together with the consideration of any contraindications or precautions, risk stratification can be used to guide surgeons in selection of the optimal prophylactic therapy for each patient.

Clinical data suggest that using nonpharmacologic measures, such as GCS and IPC, can be effective in low- and moderate-risk patients and can further enhance protection against VTE in high-risk patients when used in combination with pharmacologic agents. Pharmacologic therapies, including UFH and LMWH, are recommended for use in all high-risk (≥3 risk factors) general surgical patients. In addition, fondaparinux is an important treatment option for higher risk patients undergoing abdominal surgery, especially for cancer. It has been demonstrated that extended pharmacologic prophylaxis (up to 4 weeks) can significantly reduce the incidence of VTE events compared with prophylaxis for one week. Based on these data, it is suggested that high risk patients receive extended pharmacologic prophylaxis.

UFH is the least expensive pharmacologic agent and is safe for use in patients with renal failure and those undergoing neuraxial anesthesia. However, it is associated with HIT and must be given three times daily in patients at high risk for VTE. LMWHs have been shown to be at least as safe

and effective as UFH, are associated with a lower incidence of HIT, can be given once or twice daily, and may improve survival in patients with cancer. LMWHs should be used with caution in patients with renal failure or in those undergoing neuraxial anesthesia. Prophylactic administration of a novel factor Xa inhibitor, fondaparinux, has been shown to be as safe and at least as effective as UFH and LMWH for the prevention of VTE after abdominal surgery (see Figure 42.1) and to be significantly more effective than LMWH in cancer surgical patients. In addition, fondaparinux has an apparent lack of association with HIT and it can be given once daily. Fondaparinux has a long half-life, allowing for once-daily dosing, but this can be a disadvantage in the event of bleeding complications. In patients undergoing neuraxial anesthesia, there is a recent trial indicating that fondaparinux may be used with a longer period between spinal tap and the first injection of fondaparinux.[101] It cannot be used in patients with advanced renal failure.

There is no single method of VTE prophylaxis that is optimal for every patient. The benefits and risks of each agent should be considered for each patient so that the safest, most effective therapy is initiated. As yet, little is known about the appropriate duration of these measures; however, in selected patients at high risk for VTE, extended prophylaxis is recommended.

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CHAPTER

43

Conventional Treatment of Deep Venous Thrombosis

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INTRODUCTION

Deep vein thrombosis (DVT) and/or pulmonary embolism (PE) can be considered manifestations of the same clinical entity, venous thromboembolism (VTE). There is mounting evidence that patients who present with PE have a worse prognosis than do patients who present with symptomatic DVT; recurrence is more likely to be fatal in patients who initially present with PE.[1] Patients who present with symptomatic PE have been shown to have recurrent episodes of PE rather than DVT.[2,3] Apart from these differences the initial and long-term treatment for patients with either DVT or PE is the same with the possible exception of the use of thrombolytic therapy for patients with submassive or massive pulmonary embolism. Indeed, the recommendations for treatment of DVT and PE are similar in the recent chapter on Antithrombotic Therapy for Venous Thromboembolic Disease in the 7th ACCP Conference on Anti-Thrombotic and Thrombolytic Therapy.[4]

The objectives for the treatment of patients with VTE are to prevent the post-thrombotic syndrome, to prevent recurrent VTE, and to prevent death from PE.

In addition to the significant morbidity and decreased quality of life of patients[5] suffering from severe post-thrombotic syndrome, particularly with venous ulcers, this syndrome is associated with very significant health care costs. The use of graduated compression stockings has been shown to significantly decrease the incidence of the post-thrombotic syndrome,[6,7] but many patients still do not have these devices prescribed or do not comply with their use. In more recent years more attention has been paid to factors that predispose to the development of the post-thrombotic syndrome, which still affects a significant proportion of patients who develop proximal DVT. These factors include recurrent ipsilateral proximal DVT,[8] increased thrombus burden as measured by venography or ultrasonography,[9] poor oral anticoagulant therapy during the treatment period,[10] and early ambulation.[11]

The initial anticoagulant treatment of VTE consists of either intravenous or subcutaneous unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) with long-term anticoagulation with a vitamin K antagonist such as warfarin or acencoumarol commencing in conjunction with the heparins. This chapter will review the conventional treatment of venous thromboembolism.

UNFRACTIONATED HEPARIN THERAPY

Heparin Therapy

Unfractionated heparin has been used extensively to prevent and treat VTE. However, more recently LMWHs have been evaluated against several different controls for the same clinical problems, and in most countries LMWH has replaced UFH for the treatment of VTE in most cases either entirely or predominantly in the out-of-hospital setting. However, there are patients in whom UFH by continuous infusion continues to be used primarily because the anticoagulant effect can be reversed by stopping the intravenous infusion and/or administering protamine sulphate.[12] Such patients include critically ill patients in the intensive care unit or cardiovascular unit, patients who may be candidates for interventions requiring interruption of anticoagulant therapy, for example, for surgical procedures or thrombolysis or in patients with severe renal failure.[12] In some countries, UFH is the anticoagulant of choice for patients suffering PE who are hemodynamically unstable.

Unfractionated heparin from either porcine or bovine sources has been used clinically for several decades, yet, although studied extensively, much remains uncertain about heparin's mode of action, particularly those related to its nonanticoagulant properties.

The anticoagulant activity of UFH depends upon a unique pentasaccharide, which binds to antithrombin and potentiates the inhibition of thrombin and activated factor X (Xa) by antithrombin.[12–14] About one-third of all heparin molecules contain the unique pentasaccharide sequence.[12–14] It is the pentasaccharide sequence that confers the molecular high affinity for antithrombin.[12–14] In addition, heparin catalyzes the inactivation of thrombin by another plasma co-factor, (co-factor II), which acts independently of antithrombin.[12]

Heparin has a number of other effects.[13] These include the release of tissue factor pathway inhibitor, binding to numerous plasma and platelet proteins, endothelial cells, and leukocytes, suppression of platelet function and an increase in vascular permeability. The anticoagulant response to a standard dose of heparin varies widely between patients. This makes it necessary to monitor the anticoagulant response of heparin, using either the activated partial thromboplastin time (APTT) or heparin levels and to titrate the dose to the individual patient.[12]

One accepted approach to anticoagulant therapy for VTE is a combination of continuous intravenous heparin and oral warfarin. The length of the initial intravenous heparin therapy has been reduced to five days, thus shortening the hospital stay and leading to significant cost saving.[15,16] The simultaneous use of initial heparin and warfarin has become clinical practice for all patients with venous thromboembolism who are medically stable.[12] Exceptions include patients who require immediate medical or surgical intervention, such as in thrombolysis or insertion of a vena cava filter, or patients at very high risk of bleeding. Heparin is continued until the INR has been within the therapeutic range (2 to 3) for two consecutive days.[12]

It has been established from experimental studies and clinical trials that the efficacy of heparin therapy depends upon achieving a critical therapeutic level of heparin within the first 24 hours of treatment.[17–19] Data from double blind clinical trials indicate that failure to achieve the therapeutic APTT threshold by 24 hours was associated with a 23.3% subsequent recurrent venous thromboembolism rate, compared with a rate of 4 to 6% for the patient groups who were therapeutic at 24 hours.[18,19] The recurrences occurred throughout the three-month follow-up period and could not be attributed to inadequate oral anticoagulant therapy.[18] The critical therapeutic level of heparin, as measured by the APTT, is 1.5 times the mean of the control value or the upper limit of the normal APTT range.[17–19] This corresponds to a heparin blood level of 0.2 to 0.4 U/ml by the protamine sulphate titration assay, and 0.35 to 0.70 by the anti-factor Xa assay.

However, there is wide variability in the APTT and heparin blood levels with different reagents and even with different batches of the same reagent.[12,20] It is, therefore, vital for each laboratory to establish the minimal therapeutic level of heparin, as measured by the APTT, that will provide a heparin blood level of at least 0.35 U/ml by the anti-factor Xa assay for each batch of thromboplastin reagent being used, particularly if a new batch of reagent is provided by a different manufacturer.[12]

Although there is a strong correlation between subtherapeutic APTT values and recurrent thromboembolism, the relationship between supratherapeutic APTT (APTT ratio 2.5 or more) and bleeding is less definite.[18] Indeed, bleeding during heparin therapy is more closely related to underlying clinical risk factors than to APTT elevation above the therapeutic range.[18] Weight and age >65 are independent risk factors for bleeding on heparin.

Numerous audits of heparin therapy indicate that administration of intravenous heparin is fraught with difficulty, and that the clinical practice of using an *ad hoc* approach to heparin dose-titration frequently results in inadequate therapy. The use of a prescriptive approach or protocol for administering intravenous heparin therapy has been evaluated in two prospective studies in patients with venous thromboembolism.[17,19]

In one clinical trial for the treatment of DVT, patients were given either intravenous heparin alone followed by warfarin, or intravenous heparin and simultaneous warfarin.[18] The heparin nomogram is summarized in Tables 43.1 and 43.2. Only 1 and 2% of the patients were undertreated for more than 24 hours in the heparin group and in the heparin and warfarin group, respectively. Objectively documented recurrent venous thromboembolism occurred infrequently in both groups (7%), at rates similar to those previously reported. These findings demonstrated that subtherapy was avoided in most patients and that the heparin protocol resulted in effective delivery of heparin therapy in both groups.

In another clinical trial, a weight-based heparin dosage nomogram was compared with a standard-care nomogram[19] (see Table 43.3). Patients on the weight-adjusted heparin nomogram received a starting dose of 80 U/kg as a bolus and 18 U/kg/h as an infusion. The heparin dose was adjusted to maintain an APTT of 1.5 to 2.3 times control. In the weight-adjusted group, 89% of patients achieved the therapeutic range within 24 hours compared with 75% in the standard-care group. Recurrent VTE was more frequent in the standard-care group; supporting the previous observation that subtherapeutic heparin during the initial 24 hours is associated with a higher incidence of recurrences. This study included patients with unstable angina and arterial thromboembolism in addition to VTE, which suggests that the principles applied to a heparin nomogram for the treatment of VTE, may be generalizable to other clinical conditions.

TABLE 43.1 Heparin Protocol

1. Administer initial intravenous heparin bolus: 5000 U.
2. Administer continuous intravenous heparin infusion: commence at 42 mL/h of 20,000 U (1680 U/h) in 500 mL of two-thirds dextrose and one-third saline (a 24-hour heparin dose of 40,320 U), except in the following patients, in whom heparin infusion is commenced at a rate of 31 mL/h (1240 U/h, a 24-hour dose of 29,760 U):
   1. Patients who have undergone surgery within the previous 2 weeks.
   2. Patients with a previous history of peptic ulcer disease or gastrointestional or genitourinary bleeding.
   3. Patients with recent stroke (i.e., thrombotic stroke within 2 weeks previously).
   4. Patients with a platelet count <150 $*$ 10⁹/L.
   5. Patients with miscellaneous reasons for a high risk of bleeding (e.g., hepatic failure, renal failure, or vitamin K deficiency).
3. Adjust heparin dose by use of the aPTT. The aPTT test is performed in all patients as follows:
   1. 4–6 hours after commencing heparin; the heparin dose is then adjusted.
   2. 4–6 hours after the first dosage adjustment.
   3. Then, as indicated by the nomogram for the first 24 hours of therapy.
   4. Thereafter, is once daily, unless the patient is subtherapeutic,* in which case the aPPT test is repeated 4–6 hours after the heparin dose is increased.

aPTT = activated partial thromboplastin time.

*Subtherapeutic = aPTT <1.5 times the mean normal control value for the thromboplastin reagent being used.

Adapted from Reference 17.

TABLE 43.2 Intravenous Heparin Dose Titration Nomogram According to the APTT

APTT (sec)	Rate change (ml/h)	Dose change (IU/24h)[a]	Additional action
≤45	+6	+5760	Repeated APTT[b] in 4–6 h
46–54	+3	+2880	Repeated APTT in 4–6 h
55–85	0	0	None[c]
86–110	–3	–2880	Stop heparin sodium treatment for 1 h; repeated APTT 4–6 h after restarting heparin treatment
>110	–6	–5760	Stop heparin treatment for 1 h; repeated APTT 4–6 h after restarting heparin treatment

[a]Heparin sodium concentration 20,000 IU in 500 ml–40 IU/ml.

[b]With the use of Actin-FS thromboplastin reagent (Dade, Mississauga, Ontario, Canada).

[c]During the first 24 h, repeated APTT in 4–6 h. Thereafter, the APTT will be determined once daily, unless subtherapeutic.

APTT = activated partial thromboplastin time.

Adapted from Reference 17.

TABLE 43.3 Weight-based Nomogram for Initial Intravenous Heparin Therapy (figures in parentheses show comparison with control)

	Dose (IU/kg)
Initial dose	80 bolus, then 18/h
APTT < 35 sec (<1.2×)	80 bolus, then 4/h
APTT 35–45 sec (1.2–1.5×)	40 bolus, then 2/h
APTT 46–70 sec (1.5–2.3×)	No change
APTT 71–90 sec (2.3–3.0×)	Decrease infusion rate by 2/h
APTT > 90 sec (>3.0×)	Hold infusion 1 h, then decrease infusion rate by 3/h

APTT = activated partial thromboplastin time

Adapted from Reference 19.

Continued use of the weight-based nomogram has been similarly effective.[20]

Adjusted dose subcutaneous UFH has been used in the initial treatment of VTE. One concern with giving UFH subcutaneously every 12 hours is that there is difficultly in achieving therapeutic APTT levels.[21] Indeed, that was true in a previous clinical trial comparing subcutaneous UFH with intravenous UFH where therapeutic heparin levels and APTT values were achieved at 24 hours in 37% of patients receiving subcutaneous UFH, compared with 71% of those who received intravenous UFH.[21] These findings are of concern in view of the fact that recurrent VTE occurs more frequently in patients who failed to achieve therapeutic heparin levels in terms of APTT values within the first 24 to 48 hours of therapy as compared with those who achieve therapeutic levels.[18,19]

Four randomized clinical trials compared the efficacy of subcutaneous UFH with subcutaneous LMWH in patients with proven VTE.[22–25] Nomograms have been developed for subcutaneous UFH.[26] The largest of these trials compared subcutaneous UFH dose adjusted with the use of APTT by means of a weight adjusted algorithm with fixed dose low-molecular-weight heparin for the initial treatment of patients with VTE, 16% of whom presented with PE.[25] Subcutaneous UFH was shown to be similar to fixed dose LMWH in terms of efficacy and safety.[25] It is worth noting, however, that the rate of recurrence VTE was three times lower in patients who did achieve a therapeutic APTT threshold within the first 24 hours of therapy, than in those who did not, similar to results from previous studies.[25]

COMPLICATIONS OF HEPARIN THERAPY

The main adverse effects of heparin therapy include bleeding, thrombocytopenia, and osteoporosis. Patients at particular risk of bleeding are those who have had recent

surgery or trauma, or who have other clinical factors which predispose to bleeding on heparin, such as peptic ulcer, occult malignancy, liver disease, hemostatic defects, age >65 years, and female gender.

The management of bleeding on heparin will depend on the location and severity of bleeding, the risk of recurrent VTE and the APTT; heparin should be discontinued temporarily or permanently. Patients with recent VTE may be candidates for insertion of an inferior vena cava filter. If urgent reversal of heparin effect is required, protamine sulphate can be administered.[12]

Heparin-induced thrombocytopenia is a well-recognized complication of heparin therapy, usually occurring within five to 10 days after heparin treatment has started.[27,28] Approximately 1 to 2% of patients receiving unfractionated heparin will experience a fall in platelet count to less than the normal range or a 50% fall in the platelet count within the normal range. In the majority of cases, this mild to moderate thrombocytopenia appears to be a direct effect of heparin on platelets and is of no consequence. However, approximately 0.1 to 0.2% of patients receiving heparin develop an immune thrombocytopenia mediated by IgG antibody directed against a complex of PF4 and heparin.[29] In some cases neutrophil acting peptide 2 (NAP-2) and interleukin 8 (IL8) also play a role in pathogenesis.

The incidence of heparin-induced thrombocytopenia (HIT) is lower with the use of LMWH;[28,30] however, the clinical manifestations may be as or more severe than those seen with UFH.[31] Furthermore, the nadir of the platelet count, onset, and duration of thrombocytopenia have been shown to be somewhat different.[32] Recently, delayed onset of HIT has been described with the onset being as long as several weeks after the end of exposure to heparin, thus, making this syndrome sometimes more difficult to diagnose.[33] Furthermore, the incidence and severity of HIT varies among different patient populations being more prevalent in patients having cardiac or orthopedic procedures than for medical patients.[34] The development of thrombocytopenia may be accompanied by arterial or DVT, which may lead to serious consequences such as death or limb amputation.[27,34]

When a clinical diagnosis of HIT is made heparin in all forms must be stopped immediately. In most centers the confirmatory laboratory test is an ELISA assay for the PF4-heparin complex, but, where possible, this should be confirmed with a functional assay, such as the serotonin release assay.[34] In those patients requiring ongoing anticoagulation, an alternative form of anticoagulation must be undertaken immediately because of the high incidence of thrombosis when heparin is stopped.[35] Some authorities recommend the use of alternative anticoagulants in all patients once a diagnosis is made. The most common alternative agents are the specific antithrombin argatroban[34,35,36] or the direct thrombin inhibitor lepirudin.[35,38,39] Both agents are given by intravenous infusion. Lepirudin has the advantage that it can be given to patients with renal insufficiency,[34,35] but it has the disadvantage that with prolonged use antibodies develop and some of these can have serious deleterious effects, including anaphylaxis.[40,41,42] Argatroban is primarily excreted by the kidney so that it cannot be used in people with severe renal failure but it can be used in patients with significant hepatic insufficiency.[34,35,36] Both agents can be used in conjunction with vitamin K antagonists but it should be noted that argatroban by itself increases the INR beyond that observed with warfarin alone and this must be taken into account in controlling the vitamin K antagonist.[37] The alternative antithrombotic agents should be continued until the platelet count is at least back to 100×10^9/L and/or the INR is therapeutic for two consecutive days.[34] Danaparoid has been used in the past but is no longer available for many countries. The pentasaccharide fondaparinux has been used as an alternative antithrombotic agent in HIT patients and it has the advantage that it is given by a once daily subcutaneous injection.[43,44] Insertion of an inferior vena cava filter is seldom indicated.

Osteoporosis has been reported in patients receiving unfractionated heparin in dosages of 20,000 U/day (or more) for more than six months.[12] Demineralization can progress to the fracture of vertebral bodies or long bones, and the defect may not be entirely reversible.[12] Laboratory and clinical studies indicate that the incidence of osteoporosis with use of long-term LMWH is low.[12]

LOW-MOLECULAR-WEIGHT HEPARIN (LMWH) FOR THE INITIAL TREATMENT OF VTE

Heparin currently in use clinically is polydispersed unmodified heparin, with a mean molecular weight ranging from 10 to 16 kDa. Low molecular weight derivatives of commercial heparin have been prepared that have a mean molecular weight of 4–5 kDa.[45,46]

The LMWHs commercially available are made by different processes (such as nitrous acid, alkaline, or enzymatic depolymerization) and they differ chemically and pharmacokinetically.[45,46] The clinical significance of these differences, however, is unclear, and there have been very few studies comparing different LMWHs with respect to clinical outcomes.[46] The doses of the different LMWHs have been established empirically and are not necessarily interchangeable. Therefore, at this time, the effectiveness and safety of each of the LMWHs must be tested separately.[46]

The LMWHs differ from unfractionated heparin in numerous ways. Of particular importance are the following: increased bioavailability (>90% after subcutaneous injection), prolonged half-life and predictable clearance enabling once- or twice-daily injection, and predictable antithrombotic response based on body weight permitting treatment

without laboratory monitoring.[12,45,46] Other possible advantages are their ability to inactivate platelet-bound factor Xa, resistance to inhibition by platelet factor IV and their decreased effect on platelet function and vascular permeability (possibly accounting for less hemorrhagic effects at comparable antithrombotic doses).

There has been a hope that the LMWHs will have fewer serious complications such as bleeding, heparin-induced thrombocytopenia and osteopenia, when compared with unfractionated heparin.[45,47] Evidence is accumulating that these complications are indeed less serious and less frequent with the use of LMWH. LMWH has been approved for the prevention and treatment of venous thromboembolism in pregnancy. These drugs do not cross the placenta and large case series suggest they may be both effective and safe. The LMWHs all cross-react with unfractionated heparin; therefore they cannot be used as alternative therapy in patients who develop heparin-induced thrombocytopenia. The heparinoid danaparoid possesses a 10 to 20% cross-reactivity with heparin and it can be used safely in patients who have no cross-reactivity.

Four LMWHs are approved for clinical use in Canada, and three LMWHs have been approved for use in the United States.

In a number of early clinical trials (some of which were dose-finding), LMWH given by subcutaneous or intravenous injection was compared with continuous intravenous unfractionated heparin with repeat venography at day 7 to 10 being the primary endpoint.[12] These studies demonstrated that LMWH was at least as effective as unfractionated heparin in preventing extension or increasing resolution of thrombi on repeat venography.

Subcutaneous unmonitored LMWH has been compared with continuous intravenous heparin in a number of clinical trials for the treatment of proximal DVT using long-term follow-up as an outcome measure.[48–51,55–57] These studies have shown that LMWH is at least as effective and safe as unfractionated heparin in the treatment of proximal DVT. Pooling of the most methodologically sound studies suggests a significant advantage for LMWH in the reduction of major bleeding and mortality.[52,53] Further recent studies have indicated that LMWH used predominantly out-of-hospital was as effective and safe as intravenous unfractionated heparin given in-hospital.[55–57] Two clinical trials showed that LMWH was as effective as intravenous heparin in the treatment of patients presenting with PE.[54,58] Economic analysis of treatment with LMWH versus intravenous heparin demonstrated that LMWH was cost-effective for treatment in-hospital as well as out-of-hospital.[59] As these agents have become more widely available for treatment, they have replaced intravenous unfractionated heparin in the initial management of patients with VTE.

Long-term LMWH has been compared with warfarin therapy in patients presenting with proximal DVT.[60] Although these studies differ in design and doses of LMWH, they do indicate that LMWH is a useful alternative to warfarin therapy, particularly in patients who have recurrence of VTE while on therapeutic doses of warfarin (e.g., in the cancer population).[60] More recently long-term low-molecular-weight heparin has been compared with long-term vitamin K antagonists for the treatment of a broad spectrum of patients and patients presenting with cancer and proximal DVT.[61,62] In the latter study there was a significant decrease in the incidence of recurrent VTE with the use of long-term LMWH[62] and in the former study involving a broad spectrum of patients including those with cancer, there was a significant decrease in the incidence of bleeding complications.[62] Based on these trials, LMWH has been recommended for a period of at least three to six months for patients presenting with VTE or PE and cancer.[4]

ANTICOAGULANT THERAPY: WARFARINS AND RELATED COMPOUNDS (VITAMIN K ANTAGONISTS)

Warfarin and related compounds have been shown to be efficacious and safe in a wide variety of clinical thrombotic disorders including venous thromboembolism, stroke prevention in nonvalvular atrial fibrillation, and prevention of systemic emboli in patients who have myocardial infarction or prosthetic heart valves. Although low-molecular-weight heparin has been shown to be efficacious and safe in the long-term treatment of venous thromboembolism particularly in patients with cancer, wafarin and related vitamin K antagonists remain the treatment of choice for the long-term treatment of venous thromboembolism.

PHARMACOLOGY

The Vitamin K Cycle

Vitamin K is responsible for the post-translational conversion of glutamate residues into Gla in a limited number of proteins, the best known of which are the blood coagulation factors II, VII, IX, X, protein C, protein S, and protein Z, and bone matrix proteins. The best-known bone matrix proteins are osteocalcin and matrix Gla-protein (MGP).[63]

γ-Carboxyglutamic acid permits the binding of calcium by these proteins, and in the presence of calcium the coagulation factors undergo a conformational change that is required for their binding to various active cofactors on cell surfaces.[64] The reduced form of vitamin K (KH_2) acts as a coenzyme for carboxylase. The oxidation of vitamin K (KH_2) by oxygen into vitamin K epoxide (KO) provides energy to fix carbon dioxide (CO_2) at the γ-position of a glutamate residue (see Figure 43.1). The vitamin KO is then recycled, first by

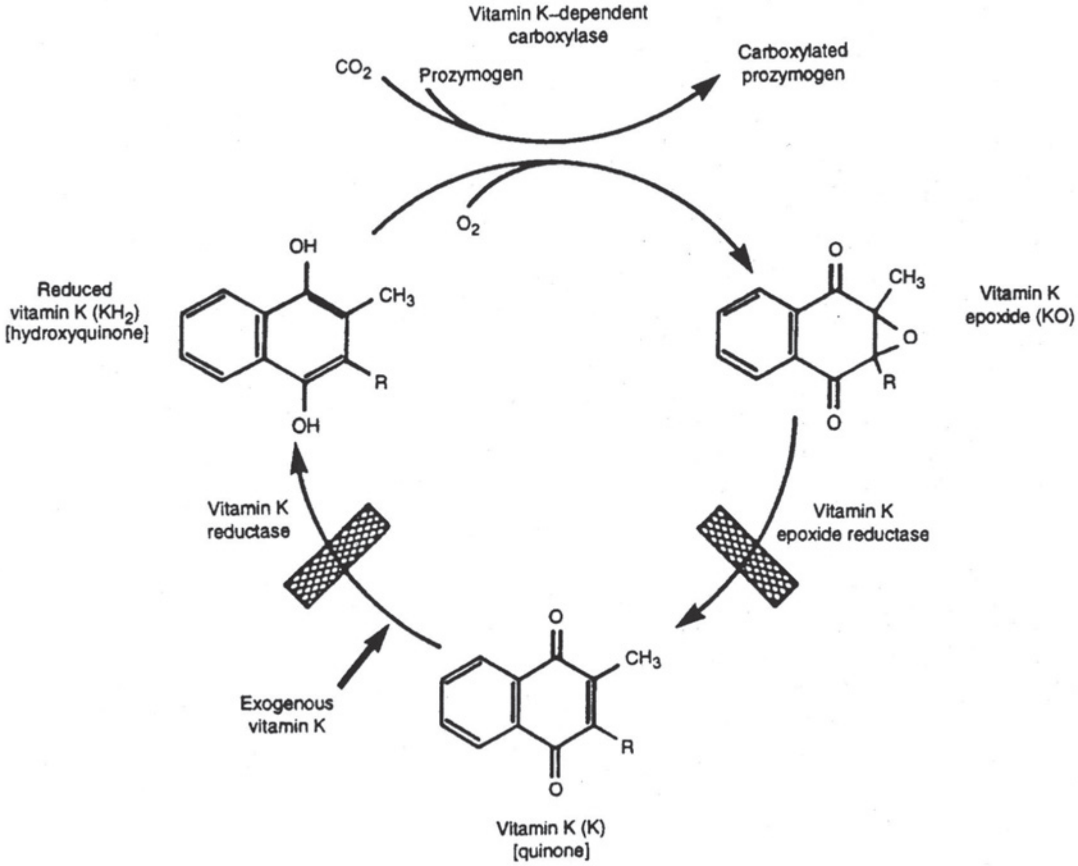

FIGURE 43.1 The vitamin K cycle: the effect of warfarin and exogenous vitamin K (phytomenadione). Vitamin K (quinone) is covered to reduce vitamin K ($KH_{2,}$ hydroxyquinone) by vitamin K reductase. Vitamin KH_2 is the substrate for the carboxylation of prozymogens (e.g., factor II, VII, IX, X) to activate enzymes. Carbon dioxide and oxygen are required for this reaction, and vitamin KH_2 is converted to vitamin K epoxide (KO). Vitamin K is regenerated for vitamin KO by vitamin K epoxide reductase. Warfarin inhibits vitamin K epoxide reductase and, to some extent, vitamin K reductase (*hatched areas*). Exogenous vitamin K in large doses overcomes the blockage by warfarin, presumably because vitamin K reductase is less sensitive to warfarin than is vitamin K expoxide reductase (*arrow*). Reproduced from reference 64, with permission.

vitamin K epoxide reductase to vitamin K (quinone) and then by vitamin K reductase to vitamin KH_2 (hydroquinone). It is essential that each molecule of vitamin K is recycled several hundred times before being metabolized.

The oral anticoagulants inhibit vitamin KO reductase and possibly vitamin K reductase, thereby depleting vitamin KH_2 and causing the buildup of vitamin KO in the tissues such as the liver and plasma (see Figure 43.1).

The most important forms of vitamin K are phylloquinones (vitamin K_1) and menaquinones (vitamin K_2).[63] Phylloquinones are found in green, leafy vegetables such as spinach, cabbage, and broccoli. Deficiencies of these vegetables in the diet can cause vitamin K deficiency, whereas excessive amounts can reverse the effects of oral anticoagulants. The menaquinones occur in various foods such as yogurt and organ meats. They are also produced by the bacterial flora of the colon and possibly the small intestine. Factors interfering with the production or absorption of these menaquinones, for example, broad-spectrum antibiotics, may lead to vitamin K deficiency[65] and interference with anticoagulant control. Also, certain cephalosporins containing a N-methyl-thiotetrazole side chain may interfere directly with vitamin KO reductase in the liver,[66] thereby leading to vitamin K deficiency. Most of the vitamin K stores in the liver are menaquinones and it is thought that most of these originate from the diet rather than intestinal flora.[63]

Large doses of vitamin K can overcome the blockade of vitamin KH_2 by oral anticoagulants presumably because vitamin K reductase is less sensitive to the coumarins than is vitamin KO reductase (see Figure 43.1).[63] This reversal of oral anticoagulants applies to the first generation agents such as warfarin, but does not apply to the second generation rodenticides known as the super warfarins, which have an extremely long half-life. Accidental consumption of these

agents requires repeated injections of vitamin K and fresh frozen plasma for a prolonged period of time to completely overcome their effects.[67,68]

Pharmacokinetics and Pharmacodynamics of Warfarin

There are two distinct chemical groups of oral anticoagulants: the 4-hydroxy coumarin derivatives (e.g., warfarin sodium) and the indane-1, 3-dione derivatives (e.g., phenindione).[69] The coumarin derivatives are the oral anticoagulants of choice because they are associated with fewer nonhemorrhagic side effects than are the indanedione derivatives. In North America the most commonly used agent is coumarin (Bristol-Myers Squibb), but in recent years various generic forms of warfarin sodium have been introduced.

Warfarin is a racemic mixture of stereo-isomers (R & S forms). Warfarin is highly water soluble and is highly bioavailable.[70] Peak absorption occurs around 90 minutes and the half-life is between 36 and 42 hours. Warfarin is highly protein bound (primarily albumen), and only the nonprotein bound material is biologically active. Any drug or chemical, which is also bound to albumen, may displace warfarin from its protein binding sites and thereby increase the biologically active material.[70] Warfarin is metabolized in the liver by the p450 system of enzymes. Interference with the p450 enzymes by various drugs or a mutation in the gene coding for one of the common p450 enzymes can markedly interfere with the metabolism of warfarin. Therefore, the half-life of warfarin can vary markedly from one patient to another and individual laboratory monitoring to determine drug dosing is mandatory.

The anticoagulant effect of warfarin is mediated by the inhibition of the vitamin K-dependent gamma-carboxylation of coagulation factors II, VII, IX, and X.[69,70] This results in the synthesis of immunologically detectable but biologically inactive forms of these coagulation proteins. Warfarin also inhibits the vitamin K-dependent gamma-carboxylation of proteins C and S.[71] Protein C circulates as a proenzyme that is activated on endothelial cells by the thrombin/thrombomodulin complex to form activated protein C. Activated protein C in the presence of protein S inhibits activated factor VIII and activated factor V activity.[71] Therefore, vitamin K antagonists such as warfarin create a biochemical paradox by producing an anticoagulant effect due to the inhibition of pro-coagulants (factors II, VII, IX, and X) and a potentially thrombogenic effect by impairing the synthesis of naturally occurring inhibitors of coagulation (proteins C and S).[71,72] Heparin or low molecular weight heparin and warfarin treatment should overlap by four to five days when warfarin treatment is initiated in patients with thrombotic disease.[73]

The anticoagulant effect of warfarin is delayed until the normal clotting factors are cleared from the circulation, and the peak effect does not occur until 36 to 72 hours after drug administration.[74–76] During the first few days of warfarin therapy, the prothrombin time (PT) reflects mainly the depression of factor VII which has a half-life of five to seven hours. Equilibrium levels of factors II, IX, and X are not reached until about one week after the initiation of therapy.[75–77] The use of small initial daily doses (e.g., 5 mg) is the preferred approach for initiating warfarin treatment.[70,78] The dose-response relationship to warfarin therapy varies widely between individuals and, therefore, the dose must be carefully monitored to prevent overdosing or underdosing.

A number of factors influence the anticoagulant response of warfarin in individual patients; these include inaccuracies in laboratory testing and noncompliance of patients, but more importantly reflect the influence of dietary changes or the influence of drugs that interfere with the metabolism of warfarin. The availability of vitamin K can be influenced by dramatic changes in dietary intake[79,80] or by drugs such as antibiotics,[81–83] which interfere with the synthesis of vitamin K in the gastrointestinal tract. A wide variety of drugs may interact with warfarin.[70] However, a critical appraisal of the literature reporting such interactions indicates that the evidence substantiating many of the claims is limited.[84] The interactions of drugs and food with warfarin are reviewed in detail elsewhere.[70] Aspirin is particularly problematic because it interferes with platelet function, displaces warfarin from its protein binding thus augmenting its biological activities, and as with the NSAIDs it may cause gastric erosions thus creating a site for bleeding. Nonetheless, in certain patients the use of aspirin and warfarin is indicated to improve efficacy even though minor bleeding may be somewhat increased. It is important that patients be warned against taking any new drugs without the knowledge of their attending physician and it is prudent to monitor the INR more frequently when any drug (including natural compounds)[85] is added or withdrawn from the regimen of the patient being treated with an oral anticoagulant.

Laboratory Monitoring and Therapeutic Range

The laboratory test most commonly used to measure the effects of warfarin is the one-stage PT test. The PT is sensitive to reduced activity of factors II, VII, and X but is insensitive to reduced activity of factor IX. Confusion about the appropriate therapeutic range has occurred because the different tissue thromboplastins used for measuring the PT vary considerably in sensitivity to the vitamin K-dependent clotting factors and in response to warfarin.[86,87] Rabbit brain thromboplastin, which has been widely used in North America, is less sensitive than is standardized human brain thromboplastin, which has been widely used in the United Kingdom and other parts of Europe. A PT ratio of 1.5 to 2.0 using rabbit brain thromboplastin is equivalent to the current

therapeutic range (i.e., INR 2.0 to 3.0).[86,87] Conversely, a two- to three-fold increase in the PT using standardized human brain thromboplastin is equivalent to a 1.25- to 1.5-fold increase in the PT using a rabbit brain thromboplastin such as Simplastin or Dade-C.[86,87]

In order to promote standardization of the PT for monitoring oral anticoagulant therapy, the World Health Organization (WHO) developed an international reference thromboplastin from human brain tissue and recommended that the PT ratio be expressed as the International Normalized Ratio or INR.[70] The INR is the PT ratio obtained by testing a given sample using the WHO reference thromboplastin. For practical clinical purposes, the INR for a given plasma sample is equivalent to the PT ratio obtained using a standardized human brain thromboplastin known as the Manchester Comparative Reagent, which has been widely used in the United Kingdom. In recent years thromboplastins with a high sensitivity have been commonly used. In fact many centers have been using the recombinant tissue factor, which has an ISI value 0.9 to 1.0, giving an INR equivalent to the prothrombin time ratio.

Warfarin is administered in an initial dose of 5 to 7.5 mg per day for the first two days, and the daily dose is then adjusted according to the INR. Heparin or low-molecular-weight heparin therapy is discontinued on the fourth or fifth day following initiation of warfarin therapy, provided the INR is prolonged into the recommended therapeutic range (INR 2.0 to 3.0) for at least two consecutive days.[4] Because some individuals are either fast or slow metabolizers of the drug, the selection of the correct dosage of warfarin must be individualized. Therefore, frequent INR determinations are required initially to establish therapeutic anticoagulation.

Once the anticoagulant effect and patient's warfarin dose requirements are stable, the INR should be monitored every one to three weeks throughout the course of warfarin therapy. However, if there are factors that may produce an unpredictable response to warfarin (e.g., concomitant drug therapy), the INR should be monitored more frequently to minimize the risk of complications due to poor anticoagulant control.[70,88]

ADVERSE EFFECTS OF ORAL ANTICOAGULANTS

Bleeding

The major side effect of oral anticoagulant therapy is bleeding.[70,87,88] A number of risk factors have been identified that predispose to bleeding on oral anticoagulants.[88,89,90] The most important factor influencing bleeding risk is the intensity of the INR.[87–90] Other factors include a history of bleeding, previous history of stroke or myocardial infarction, hypertension, renal failure, diabetes, and a decreased hematocrit.[89] Efforts have been made to quantify the bleeding risk according to these underlying clinical factors.[89,90] Introduction of a multicomponent intervention combining patient education and alternative approaches to the maintenance of the INR resulted in a reduced frequency of major bleeding in the patients in this group.[89] Furthermore, patients in the intervention group were within the therapeutic INR a significantly greater amount of time than were patients in the standard care group. In a retrospective cohort study of patients with an INR greater than 6.0, it was shown that a prolonged delay in the return of the INR to the therapeutic range was seen in patients who had an INR over 4.0 after two doses of warfarin were withheld, patients with an extreme elevation of the INR, and older age patients, particularly those with decompensated congestive heart failure and active cancer.[90] Numerous randomized clinical trials have demonstrated that clinically important bleeding is lower when the targeted INR is 2.0 to 3.0, and that bleeding increases exponentially when the INR increases above 4.5 or 5.0.[87,90,91] There is a strong negative relationship between the percentage of time that patients are within the targeted INR and both bleeding and recurrent thrombosis.

Oral anticoagulant therapy in elderly patients presents further problems.[92,93,94] Many of these patients require long-term anticoagulants because of their underlying clinical conditions that increase with age, while they are more likely to have underlying causes for bleeding including the development of cancer, intestinal polyps, renal failure, and stroke, and they are more prone to having frequent falls. The daily requirements for warfarin to maintain the therapeutic INR also decreases with age, presumably due to decreased clearance of the drug. Therefore, before initiating oral anticoagulant treatment in elderly patients, the risk/benefit ratio of treatment must be considered. If they are placed on oral anticoagulant therapy, careful attention to the INR is required.

Patients with cancer are more likely to bleed on oral anticoagulant treatment.[95] Compared with patients on oral anticoagulants who do not have cancer, patients with cancer have a higher incidence of both major and minor bleeding and anticoagulant withdrawal is more frequently due to bleeding. Patients with cancer have a higher thrombotic complication rate and a higher bleeding rate regardless of the INR, whereas bleeding in noncancer patients was seen only when the INR was greater than 4.5. Safer and more effective anticoagulant therapy is required for the treatment of VTE in patients with cancer.[95]

Management of Over-Anticoagulation

The approach to the patient with an elevated INR depends on the degree of elevation of the INR and the clinical circumstances.[70,96] Options available to the physician include temporary discontinuation of warfarin treatment, admini-

stration of vitamin K or administration of blood products such as fresh frozen plasma or prothrombin concentrate to replace the vitamin K–dependent clotting factors or administration of activated Factor VII. If the increase is mild and the patient is not bleeding, no specific treatment is necessary other than reduction in the warfarin dose. The INR can be expected to decrease during the next 24 hours with this approach. With more marked increase of the INR in patients who are not bleeding, treatment with small doses of vitamin K_1 (e.g., 1 mg), given either orally or by subcutaneous injection should be considered.[97,98] With very marked increase of the INR, particularly in a patient who is either actively bleeding or at risk for bleeding, the coagulation defect should be corrected. Vitamin K can be given by the intravenous or subcutaneous route or by the oral route.[70,96] Where possible the oral route is preferred. If ongoing anticoagulation with warfarin is planned, then repeated small doses of vitamin K should be given, so that there is no problem with warfarin resistance.[70,96,97]

Reported side effects of vitamin K include flushing, dizziness, tachycardia, hypotension, dyspnea, and sweating.[70] Intravenous administration of vitamin K_1 should be performed with caution to avoid inducing an anaphylactoid reaction. The risk of anaphylactoid reaction can be reduced by slow administration of vitamin K_1. In most patients, intravenous administration of vitamin K_1 produces a demonstrable effect on the INR within six to eight hours and corrects the increased INR within 12 to 24 hours. Because the half-life of vitamin K_1 is less than that of warfarin sodium, a repeat course of vitamin K_1 may be necessary. If bleeding is very severe and life threatening, vitamin K therapy can be supplemented with concentrates of Factors II, VII, IX, and X.

When bleeding occurs in a patient on oral anticoagulants it is important to consider the site of bleeding. Bleeding from the upper gastrointestinal tract commonly is seen in patients on oral anticoagulants, and the concomitant use of other medications is often an association. When the bleeding is controlled, it is important to carry out the necessary investigations to identify bleeding lesions in the gastrointestinal or genitourinary tract, which are often unsuspected.[98]

Management of Patients Receiving Long-term Anticoagulants Who Require Temporary Interruption Therapy

Patients on long-term oral anticoagulant therapy may require a temporary interruption of therapy for surgical interventions, which may vary from dental extractions to major surgery. In such cases the risk of arterial or venous thromboembolism after anticoagulants have been discontinued must be weighed against the risk of bleeding if UFH or LMWH is used for bridging anticoagulant therapy.[70,99] In the absence of randomized clinical trials recommendations are based on large, nonrandomized cohort studies,[99] which in recent years have used low-molecular-weight heparin for bridging therapy.[100,101] These studies have shown that LMWH given in either prophylactic or therapeutic doses are effective and safe for bridging therapy. In addition this therapy is cost effective when compared with UFH in hospital.[102,103] Thus, based on the current evidence recommendations can be made depending on the anticipated risk of thromboembolism and the risk of major bleeding with anticoagulant therapy. These recommendations range from temporary lowering of the INR for certain procedures such as dental extraction to discontinuation of oral anticoagulant therapy and bridging with either unfractionated heparin or low-molecular-weight heparin in either prophylactic or therapeutic doses until a therapeutic INR is reached post-operatively.

Long-term Treatment of VTE

Patients with established DVT or PE require long-term anticoagulant therapy to prevent recurrent disease.[70] Warfarin therapy is highly effective and is preferred in most patients. Adjusted dose subcutaneous heparin or LMWH is the treatment of choice where long-term oral anticoagulants are contraindicated, such as in pregnancy or for the long-term treatment of patients in whom oral anticoagulant therapy proves to be very difficult to control. In patients with proximal DVT, long-term therapy with warfarin reduces the frequency of objectively documented recurrent VTE from 47% to 2%.[104]

There have been attempts to improve the safety of warfarin therapy by using a lower INR target, but this results in an increased thrombotic risk.[105] Although long-term treatment with warfarin to a target INR of 1.5 to 2.0 in patients who have venous thromboembolism proved to be more effective than placebo treatment,[106] a similar study that compared a target INR of 1.5 to 2.0 the standard INR of 2.0 to 3.0 showed significantly lower recurrence rate with the standard treatment, with no added risk of bleeding.[107] A number of other studies using less-intense warfarin (e.g., for the prevention of thrombobosis in central venous catheters) showed such treatment to be ineffective.[108–110] In some cases, the target INR is greater than 3.0. For example, based on retrospective studies, patients who have mechanical heart valves have been treated with a target INR of 2.5 to 3.5. In patients who have bioprosthetic heart valves or in low-risk patients who have bileaflet mechanical valves in the aortic position, the target INR is still 2.0 to 3.0.[111] Although retrospective studies suggested that patients who have antiphospholipid antibodies and recurrent thrombosis required an INR of greater than 3.0,[106–108] two randomized studies comparing an INR of 2.0 to 3.0 with an INR of 3.1 to 4.0 showed that the incidence of recurrent thrombosis and major bleeding was comparable in the two groups.[112,113]

Optimal Duration of Oral Anticoagulants after a First Episode of Venous Thromboembolism

It has been recommended that all patients with a first episode of VTE receive warfarin therapy for at least three to six months. Attempts to decrease the treatment to four weeks[114,115] or six weeks[116] resulted in higher rates of recurrent VTE in comparison with either 12 or 24 weeks of treatment (11 to 18% recurrent VTE in the following one to two years). Most of the recurrent thromboembolic events occurred in the six to eight weeks immediately after anticoagulant treatment was stopped, and the incidence was higher in patients with continuing risk factors, such as cancer and immobilization.[115,116] Treatment with oral anticoagulants for six months[116] reduced the incidence of recurrent thromboembolic events, but there was a cumulative incidence of recurrent events at two years (11%) and an ongoing risk of recurrent VTE of approximately 5 to 6% per year. In patients with a first episode of idiopathic VTE treated with intravenous heparin followed by warfarin for three months, continuation of warfarin for 24 months led to a significant reduction in the incidence of recurrent DVT when compared with placebo.[117] In a further recent trial comparing three months with 12 months of oral anticoagulant therapy after the occurrence of a first episode of idiopathic proximal DVT it was shown that patients treated for three months had a higher incidence of recurrence of VTE during the subsequent 12 months compared with those patients who were continued on anticoagulants for 12 months.[118] However, the cumulative hazard of recurrent VTE at 36 months was the same in both groups. The incidence of recurrence after discontinuation of treatment was 5.1% per patient year in patients where oral anticoagulant therapy was discontinued after three months and 5.0% per patient year in patients who received an additional nine months of oral anticoagulant therapy. The recurrence occurred in the initially unaffected leg more than half the time. This suggests that the recurrences were related to a hypercoagulable state and the duration of anticoagulant therapy did not influence the ultimate recurrence rate.[118]

Optimal Duration of Oral Anticoagulant Treatment in Patients with Recurrent VTE

In a multicenter clinical trial, Schulman et al. randomized patients with a first recurrent episode of VTE, to receive either six months or continued oral anticoagulants indefinitely, with a targeted INR of 2.0 to 2.85.[119] The analysis was reported at four years. In the patients receiving anticoagulants for six months, recurrent VTE occurred in 20.7%, compared with 2.6% of patients on the indefinite treatment ($p < .001$). However, the rates of major bleeding were 2.7% in the six months group, compared with 8.6% in the indefinite group. In the indefinite group, two of the major hemorrhages were fatal, whereas there were no fatal hemorrhages in the six month group. This study showed that extending the duration of oral anticoagulants for approximately four years resulted in a significant decrease in the incidence of recurrence, but a higher incidence of major bleeding. Without a mortality difference, the risk of hemorrhage versus the benefit of decreased recurrent thromboembolism with the use of extended warfarin treatment remains uncertain and will require further clinical trials.

From the Seventh American College of Chest Physicians Conference on Anti-thrombotic and thrombolytic Therapy the following recommendations are made.[4] Oral anticoagulant therapy should be continued for at least three months to prolong the prothrombin time to a targeted INR of 2.5 (range 2.0 to 3.0). Patients with reversible or time-limited risk factors can be treated for three to six months. Patients with a first episode of idiopathic VTE should be treated for at least six months. Patients with recurrent VTE or a continuing risk factor such as cancer, antithrombin deficiency, or the antiphospholipid syndrome, should be treated for at least 12 months and considered for indefinite long-term therapy. Patients with activated protein C resistance (Factor V Leiden) should probably receive indefinite treatment if they have recurrent disease, are homozygous for the gene, or have multiple thrombophilic conditions. Accumulated evidence indicates that symptomatic isolated calf vein thrombosis should be treated with anticoagulants for at least three months.[4]

Alternative Approaches to the Management of Oral Anticoagulant Therapy

Anticoagulant Management Clinics

In recent years a large number of anticoagulation management clinics have been developed initially in Europe and more recently in North America. These anticoagulation management clinics provide coordinated services for patients requiring long-term anticoagulation therapy.[120,121,122] Although there have been no randomized clinical trials comparing routine medical care with care given in anticoagulant management clinics, there is evidence that patients managed in anticoagulation management clinics are within the targeted INR a larger percentage of the time and therefore there would be expected to have a decrease in the incidence of thromboembolism as well as the incidence of major bleeding.[122] Cost analysis based on the data from a number of reports comparing routine medical care with anticoagulation management clinics indicate that anticoagulant management clinics are capable of achieving cost saving that should be equal to the cost of running the clinics themselves.

Computer programs are now available for the data management for anticoagulant management clinics and one

system has been developed for the ongoing prescribing of warfarin once patients have a stable INR on at least two occasions. In an interesting report, it was shown that the computer was superior to experienced hematologists in the ordering of warfarin with a higher percentage of patients achieving their targeted INR a greater amount of time with the use of the computer program.[123]

Point of Care INR Testing

A number of instruments are now available for the measurement of capillary INRs on finger sampling of whole blood. INRs performed with these instruments compare well with venous samples, and numerous studies have indicated that many patients are capable of both self-testing and self-management of their warfarin dosing.[124–126] Indeed, some studies have indicated that self-management of warfarin therapy using point of care INR testing has resulted in higher INR compliance with fewer tests when compared with physician-managed patients.[126] Self-managed vitamin-K-antagonist therapy compared with anticoagulant clinic management resulted in improved patient outcomes. Although self-managed vitamin-K-antagonist therapy resulted in a similar level of INR control, bleeding complications occurred less frequently for self-managed patients.[127]

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CHAPTER

44

The Diagnosis and Management of Heparin-Induced Thrombocytopenia

THEODORE E. WARKENTIN

INTRODUCTION

The Vein Book would be incomplete without discussing heparin-induced thrombocytopenia (HIT), for three reasons. First, deep-vein thrombosis (DVT) is almost always initially treated with heparin, thus creating the potential for this immune-mediated adverse drug reaction. Second, venous thrombosis itself is the most common complication of HIT.[1,2] Third, the treatment of HIT-associated DVT with warfarin can precipitate severe venous limb ischemia (phlegmasia cerulea dolens), with potential for limb loss (venous limb gangrene).

Definition of HIT

HIT can be defined as any clinical event (or events) best explained by platelet-activating anti-platelet factor 4 (PF4)/heparin antibodies (HIT antibodies) in a patient who is receiving, or who has recently received, heparin.[1] In most patients, this includes a large platelet count fall that usually exceeds 50%.[1–3] The clinical importance of HIT primarily stems from its strong association with thrombosis.

PATHOGENESIS

Figure 44.1 summarizes the pathogenesis of HIT.[4] The key event is formation of platelet-activating antibodies of IgG class that recognize a "self" protein, PF4, bound to heparin. Multimolecular complexes of PF4, heparin, and IgG form on platelet surfaces, leading to platelet activation and formation of procoagulant platelet-derived microparticles, thereby stimulating hypercoagulability (increased thrombin generation). Heparin molecules bind to PF4 in relation to their chain length, perhaps explaining why unfractionated heparin (UFH) is more likely to cause HIT than low-molecular-weight heparin (LMWH).[3,5] Once triggered, the prothrombotic risk of HIT persists for several days or weeks, even after stopping heparin.[1,6]

CLINICAL PRESENTATION

The "4 T's"

Thrombocytopenia is common in heparin-treated patients, yet only a minority have HIT. A clinical scoring system, the "4 T's," helps predict which patients have HIT, based upon assessment of: *T*hrombocytopenia, *T*iming, *T*hrombosis, and the absence of o*T*her explanation(s) (see Table 44.1).[7] Evaluation of this scoring system suggests that HIT antibodies are unlikely (<5%) when a low score (≤3) is obtained, but very likely (>80%) with a high score (≥6).[8] An intermediate score (4 or 5) usually indicates a clinical profile compatible with HIT but also with another plausible explanation, such as sepsis.

Most patients with HIT have moderate thrombocytopenia, with platelet count nadirs usually between 20 to 150 × 10^9/L (median nadir, 55 × 10^9/L); only 5 to 10% develop a platelet count fall to less than 20 × 10^9/L.[1,2] At least 90% of patients evince a 50% or greater platelet count fall; especially in postoperative patients (who usually exhibit thrombocytosis after postoperative day 5), even a large platelet count fall may not necessarily cause the platelet count to fall below 150 × 10^9/L.[3]

Typically, the platelet count begins to fall five to 10 days after starting heparin, although a more rapid platelet count fall can occur if HIT antibodies are already present because of a recent exposure to heparin.[9] This link between

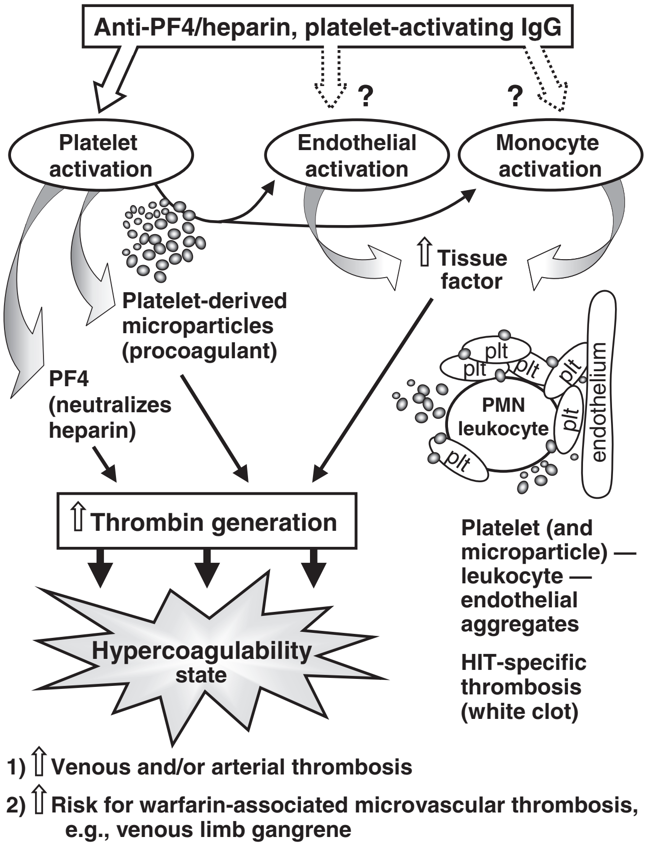

FIGURE 44.1 Pathogenesis of HIT: two explanations for thrombosis. Activation of platelets (Plt) by platelet-activating anti-platelet factor 4 (PF4)/heparin IgG antibodies (HIT antibodies), leading to formation of procoagulant, platelet-derived microparticles, and neutralization of heparin by PF4 released from activated platelets. This results in marked increase in thrombin (hypercoagulability state) characterized by an increased risk of venous and arterial thrombosis, as well as increased risk for coumarin-induced venous limb gangrene. However, it is also possible that unique pathogenetic mechanisms operative in HIT, including pancellular activation (platelets, endothelium, monocytes, neutrophils) explain unusual thromboses, such as arterial white clots. Reprinted, with permission.[4]

"rapid-onset HIT" and recent heparin use is explained by the unusual transience of HIT antibodies, which become undetectable a median of 50 to 80 days (depending on the assay performed) after an episode of HIT.[9] Indeed, the transience of HIT antibodies, together with the inability to regenerate HIT antibodies before day 5 following reexposure, provides a rationale for using heparin anticoagulation during cardiac or vascular surgery in a patient with previous HIT, provided that HIT antibodies are no longer detectable.[10]

Rarely, HIT begins several days after heparin already has been stopped (delayed-onset HIT); this syndrome is associated with strong positive tests for HIT antibodies.[11] Some sera activate platelets *in vitro* without the need to add heparin.

Thrombosis is the most important complication of HIT, and occurs in most patients.[1–3] Both venous and arterial thrombi (or both) can occur (see Table 44.2). The odds ratio for thrombosis ranges from 20 to 40.[12]

Venous Thrombosis and HIT

Venous thrombosis is the most common complication of HIT, usually manifesting as unilateral or bilateral lower-limb DVT.[1,2] Indeed, DVT occurs in about 50% of patients with HIT, with about half of these also developing symptomatic pulmonary embolism. In one study, upper-limb DVT occurred in 10% of HIT patients with use of a central venous catheter (CVC); compared with controls, both HIT and CVC use were strongly associated with upper-limb DVT, illustrating that a localizing risk factor (vessel injury from the CVC) interacts with systemic hypercoagulability (HIT), thereby influencing the type and location of thrombosis.[13]

Phlegmasia Cerulea Dolens and Venous Limb Gangrene

Venous limb ischemia (phlegmasia cerulea dolens, venous limb gangrene) can result if coumarins such as warfarin are

TABLE 44.1 Clinical Scoring System for HIT: The "4 T's"

	Points (0, 1, or 2 for each of 4 categories: maximum possible score = 8)		
	2	1	0
Thrombocytopenia	>50% platelet fall to nadir ≥20	30–50% platelet fall (or >50% fall resulting from surgical hemodilution), or nadir 10–19	<30% platelet fall, or nadir <10
Timing* of onset of platelet fall (or other sequelae of HIT)	days 5–10, or ≤ day 1 with recent heparin (past 30 days)	> day 10 or timing unclear; or < day 1 with recent heparin (past 31–100 days)	< day 4 (no recent heparin)
Thrombosis or other sequelae	proven new thrombosis; skin necrosis; or acute systemic reaction after i.v. UFH bolus	progressive or recurrent thrombosis; erythematous skin lesions; suspected thrombosis (not proven)	none
Other cause(s) of platelet fall	none evident	possible	definite
Pretest probability score: 6–8 = HIGH; 4–5 = INTERMEDIATE; 0–3 = LOW			

*First day of immunizing heparin exposure considered day 0. Reprinted, with modifications, with permission.[7]

TABLE 44.2 Thrombosis and Other Sequelae of HIT (reprinted, with modifications[2])

Venous thrombosis	Arterial thrombosis	Miscellaneous sequelae
DVT (50%): new, progressive, recurrent; lower limb (often bilateral); upper limb (at site of catheter); phlegmasia cerulea dolens	Aortic or iliofemoral thrombosis resulting in acute limb ischemia or infarction (5–10%) or spinal cord infarction (rare)	Heparin-induced skin lesions at injection sites (10–20%): erythematous plaques, skin necrosis
Coumarin-induced venous limb gangrene (5–10% of DVT treated with coumarin)	Acute thrombotic stroke (3–5%)	Coumarin-induced skin necrosis involving “central” sites (breast, abdomen, thigh, calf, etc.) (rare)
PE (25%): with or without right-sided cardiac intraatrial or intraventricular thrombi	Myocardial infarction (3–5%)	Acute systemic reactions post-i.v. heparin bolus (25% of sensitized patients receiving i.v. bolus): Inflammatory: fever, chills, flushing Cardiorespiratory: tachycardia, hypertension, dyspnea, cardiopulmonary arrest (rare) Gastrointestinal: nausea, vomiting, diarrhea Neurological: transient global amnesia, pounding headache
Cerebral (dural) sinus thrombosis (rare)	Cardiac intraventricular or intraatrial thrombosis, *in situ* or via embolization of DVT (rare)	
Adrenal hemorrhagic infarction (rare): bilateral (adrenal insufficiency) or unilateral	Thrombosis involving miscellaneous arteries (rare): upper limb, renal, mesenteric, spinal, and others	
	Embolization of thrombus from heart or proximal aorta can also contribute to microvascular ischemic syndromes	
DIC, with hypofibrinogenemia and acquired natural anticoagulant deficiency, causing multiple venous and arterial thrombi (rare)		

Estimated frequencies of the various complications of HIT are given in parentheses. Rare indicates an estimated frequency <3% of HIT patients. DIC, disseminated intravascular coagulation; DVT, deep-vein thrombosis; i.v., intravenous; PE, pulmonary embolism.

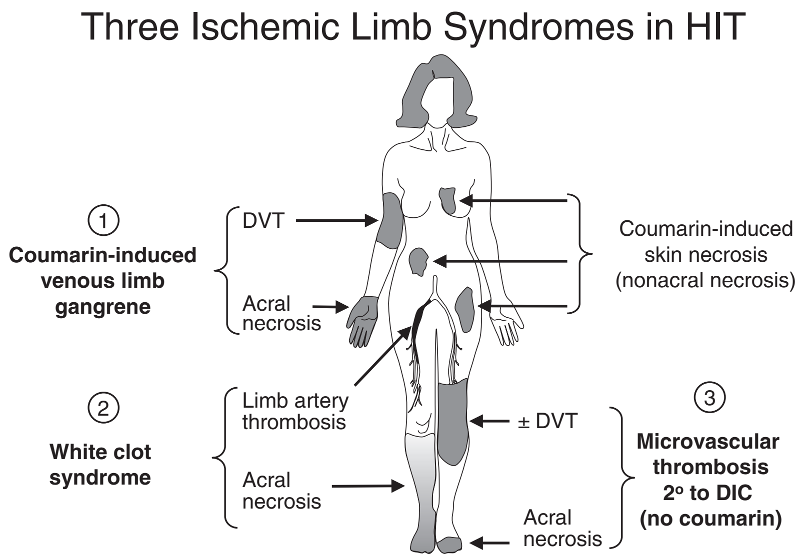

FIGURE 44.2 Three ischemic limb syndromes in HIT. ① Coumarin-induced venous limb gangrene is characterized by acral (distal extremity) necrosis in a limb with deep-vein thrombosis (DVT). The INR is usually >3.5. ② White clot syndrome is characterized by large artery occlusion by platelet-rich white clots. ③ Rarely, microvascular thrombosis secondary to disseminated intravascular coagulation (DIC) can explain acral limb necrosis even in the absence of coumarin therapy; affected limbs may or may not have associated DVT. For comparison, the classic form of coumarin-induced skin necrosis is shown, which usually involves nonacral sites, such as breast, abdomen, or thigh. Reprinted, with modifications, with permission.[15]

used to treat DVT associated with HIT (see Figure 44.2).[2,14,15] This results from disturbed procoagulant-anticoagulant balance: HIT creates hypercoagulability (increased thrombin generation) and coumarin impairs synthesis of the vitamin K-dependent natural anticoagulant, protein C. A supratherapeutic international normalized ratio (usually >3.5) is characteristic of venous limb ischemia, and represents a surrogate marker for severe protein C depletion (reflecting parallel reduction in factor VII). Rarely, overt (decompensated) disseminated intravascular coagulation (DIC) can explain microvascular thrombosis and limb ischemia in the absence of coumarin (see Figure 44.2).[2] Venous gangrene is a more common explanation for limb loss in HIT than the white clot syndrome (discussed subsequently).

Arterial Thrombosis

Occlusion of large or medium-sized arteries by platelet- and leukocyte-rich “white clots” is the classic

TABLE 44.3 Diagnostic Considerations in a Patient with Limb Ischemia and Thrombocytopenia

Concurrence of limb ischemia/necrosis and thrombocytopenia suggests one of several hematologic emergencies.

(A) HIT-associated arterial thrombosis. Occlusion of large lower-limb arteries by platelet-rich "white clots" is characteristic of heparin-induced thrombocytopenia. The major clue is an otherwise unexplained platelet count fall that begins five or more days after starting heparin. Urgent thromboembolectomy may be limb-sparing. Sensitive assays for HIT antibodies give strong positive results. See also (C).

(B) Adenocarcinoma-associated disseminated intravascular coagulation (DIC). Severe venous or arterial thrombosis can develop in patients with metastatic adenocarcinoma who have DIC, especially within hours after stopping heparin. A clinical clue is an otherwise unexplained rise in platelet count that occurred during initial heparin therapy. See also (C).

(C) Warfarin-induced phlegmasia cerulea dolens/venous limb gangrene. Coumarin anticoagulants such as warfarin can lead to venous ischemia (phlegmasia cerulea dolens) or venous limb gangrene in patients with DIC caused by HIT or adenocarcinoma. Limb loss can occur even though the limb pulses are palpable.

(D) Sepsis-associated microvascular thrombosis. Acquired natural anticoagulant failure (e.g., antithrombin or protein C depletion) can complicate DIC associated with sepsis, leading to acral limb ischemia or necrosis.

(E) Septic embolism. Rarely, infective endocarditis or aneurysmal thrombosis leads to the constellation of thrombocytopenia associated with infection and acute limb ischemia.

(F) Antiphospholipid syndrome. Autoimmune thrombocytopenia and hypercoagulability can interact to produce acute limb ischemia and thrombocytopenia in a patient with antiphospholipid syndrome.

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explanation for limb ischemia in HIT (see Figure 44.2).[2] The distal aorta and iliofemoral arteries are most frequently involved, leading to acute limb ischemia with absent pulses. The thrombi can form either *in situ* or as a result of embolization from a more proximal location, including the left ventricle or proximal aorta. Other arterial events that are common in HIT include stroke, myocardial infarction, and bowel infarction.

Limb Ischemia and Thrombocytopenia

Table 44.3 lists several diagnostic considerations when a patient presents with the combination of thrombocytopenia and an ischemic limb.[16] Absence of pedal pulses suggests occlusion of large arteries by thromboemboli. Palpable (or Doppler-identifiable) pulses, especially in the setting of DVT, suggests venous limb ischemia, due to coumarin or severe DIC (or both).

Overall, 5 to 15% of patients with HIT develop limb necrosis requiring amputation.[17,18] Sometimes, limb loss is iatrogenic (warfarin-related) and potentially preventable (see later). Timely thrombectomy can salvage limbs in some circumstances (see later).

Miscellaneous Complications

A minority of patients who develop HIT during subcutaneous (s.c.) injections of UFH or LMWH develop skin lesions at the injection sites.[1,2] Known as *heparin-induced skin lesions*, these can range from erythematous plaques to skin necrosis. Patients who develop heparin-induced skin lesions and thrombocytopenia appear to be at high risk of developing arterial thrombosis.[2] Sometimes, the platelet count fall is minimal, or begins only after heparin has been stopped.

HIT can also present as an *acute systemic reaction*.[1,2] These follow intravenous (i.v.) bolus injection of heparin to a patient with circulating HIT antibodies. Symptoms and signs, which begin five to 30 minutes post-injection, are listed in Table 44.2. Abrupt platelet count declines accompany these reactions.

Although most patients have elevated cross-linked fibrin degradation products (fibrin d-dimer), a minority with severe HIT show laboratory evidence of decompensated DIC, including elevated INR, reduced fibrinogen, red cell fragments, or circulating nucleated red cells.[2]

LABORATORY TESTING FOR HIT ANTIBODIES

Two types of assays detect HIT antibodies.[1] Most widely used are the commercial enzyme-immunoassays (EIAs) that test for antibodies reactive against PF4/polyanion complexes. In contrast, platelet activation assays exploit this pathogenic feature of HIT. As a general rule, the stronger a positive test is, the greater the likelihood the patient has HIT.[19]

Platelet Activation Assays

The best platelet activation assays utilize "washed" platelets, for example, the platelet serotonin release assay. When performed by experienced labs, this assay is sensitive for clinically important HIT antibodies, with high specificity (usually >95%), and has operating characteristics (sensitivity-specificity tradeoff) superior to the immunoassays.[19] However, washed platelet activation assays are technically demanding and available in only a few reference centers. In contrast, platelet aggregation assays that utilize a standard platelet aggregometer, and that test platelets suspended in citrate-anticoagulated plasma, have limited sensitivity and specificity.

PF4/Polyanion Immunoassays

Two commercial solid-phase EIAs detect antibodies that react with PF4 complexed with polyanion, either heparin (Stago, Asnieres, France) or polyvinyl sulfonate (Genetics Testing Institute [GTI], Waukesha, WI). Both assays detect antibodies of IgG, IgA, and IgM isotypes; however, since

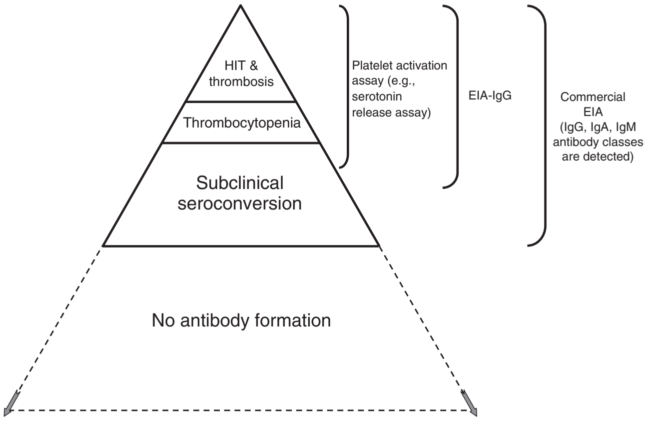

FIGURE 44.3 Iceberg model of HIT. This model depicts several features of HIT, including the hierarchy of sensitivity and specificity of three different types of assays: (i) platelet activation assay that utilizes washed platelets, for example, platelet serotonin release assay (SRA); (ii) PF4/heparin EIA that detects IgG class antibodies (EIA-IgG); and (iii) commercial EIA that detects antibodies of IgG, IgM, and/or IgA class. Clinical HIT indicates either of the top two levels of the iceberg (HIT & thrombosis; thrombocytopenia). Subclinical seroconversion indicates formation of antibodies in the absence of developing clinical HIT. The relative proportion of patients who form antibodies versus those who do not form antibodies differs in various clinical situations. Reprinted, with permission.[20]

only IgG antibodies are potentially pathogenic, including IgA and IgM can lead to false diagnosis of HIT when the thrombocytopenia is caused by another disorder.

Recently, rapid immunoassays have been developed based upon gel centrifugation technology (used in some blood banks) and particle immunofiltration technology. However, their operating characteristics remain to be defined.

Iceberg Model

Figure 44.3 shows the interrelationships among different HIT antibody assays, thrombocytopenia (clinical HIT), and HIT-associated thrombosis.[5,20] Four features are inferred: 1) both washed platelet activation assays and EIAs have similar high sensitivity for clinical HIT; 2) the washed platelet activation assays have higher diagnostic *specificity* for clinical HIT than the EIAs (although noncommercial "in-house" EIAs that only detect IgG antibodies are superior to commercial EIAs; 3) only a subset of heparin-treated patients who form platelet-activating PF4/polyanion-reactive IgG develop clinical HIT; and 4) increased risk of thrombosis is not observed in patients who develop antibodies in the absence of a significant platelet count fall.

TREATMENT

Section A of Table 44.4 lists general principles of treatment.[1,7,10] In patients strongly suspected of having HIT, all heparin should be stopped, and an appropriate nonheparin anticoagulant initiated. This recommendation applies even to patients without clinically evident thrombosis, since 25 to 50% of patients with isolated HIT develop symptomatic thrombosis (5% thrombotic death rate).[1,6]

Given the high frequency of DVT, routine duplex ultrasonography is recommended.[10] Testing for HIT antibodies provides important corroborative (if strongly positive) or contrary (if negative or only weakly positive) information. Particularly if an alternative diagnosis becomes apparent, a

TABLE 44.4 Treatment Principles When HIT Is Strongly Suspected (or Confirmed)

A. General principles
1. Discontinue and avoid all heparin (including low-molecular-weight heparin).
2. Give a nonheparin, alternative anticoagulant.
3. Postpone warfarin pending substantial platelet count recovery (give vitamin K if warfarin has already been started).
4. Test for HIT antibodies.
5. Investigate for lower-limb deep-vein thrombosis.
6. Avoid prophylactic platelet transfusions.

B. Nonheparin anticoagulant options during vascular surgery

Lepirudin

Intraoperative bolus*: 0.2–0.4 mg/kg i.v. (immediately before vascular clamping) followed by 0.05–0.10 mg/kg/h** (target APTT, 1.5–2.5× baseline);

Intraoperative "flush" solution consisting of 0.1 mg/mL lepirudin (maximum, 250 mL administered during surgery);

Postoperative anticoagulation, ranging from 0.05 mg/kg/h (target APTT 1.5–2.0× baseline APTT) or 15 mg BID s.c. in patients at relatively low risk for postoperative reocclusion (e.g., surgery involving aorta, iliac, femoral, or carotid arteries) to 0.10 mg/kg/h (target APTT 1.5–2.5× baseline) for patients at relatively high-risk of postoperative reocclusion (e.g., popliteal bypass).**

Argatroban

Intraoperative bolus*: 0.1 mg/kg bolus, followed by 2 µg/kg/min infusion (=0.12 mg/kg/h) for intraoperative and postoperative anticoagulation (target APTT 1.5–3.0× baseline APTT).

Danaparoid

Intraoperative bolus*: 2,250 anti-Xa U for patient weighing 60–75 kg (bolus dose adjusted to 1,500 and 3,000 U for patients weighing <60 and >75 kg, respectively).

Intraoperative "flush" solution: 750 U in 250 mL normal saline (maximum, 250 mL if the intraoperative bolus has been given).

Postoperative anticoagulation, ranging from low (prophylactic-dose), i.e., 750 U BID or TID s.c. or higher (therapeutic-dose) usually 200 U/h (with target anti-Xa levels between 0.5–0.8 U/mL)

*Assumes patient has absent or low drug levels at start of surgery (otherwise bolus may not be required).

**In case of renal insufficiency, dosing must be decreased by up to 90%. As anesthesia results in decreased renal perfusion, the dose of lepirudin should be reduced by approximately 30% (with APTT adjustments) during surgery and in the early postoperative period even in a patient stably anticoagulated prior to surgery. The APTT should be monitored frequently during and following surgery.

Use of these agents for intraoperative anticoagulation represents "off-label" use. References for section B are found elsewhere.[24] Section A reprinted with permission.[7]

APTT, activated partial thromboplastin time; BID, twice daily; s.c., subcutaneous; TID, thrice daily; U, units.

negative test for HIT antibodies allows for resumption of heparin.

In the United States, two nonheparin anticoagulants, lepirudin (see later) and argatroban (see later), are approved for treating thrombosis complicating HIT.[12,17,18] Other potential agents include bivalirudin, danaparoid, and fondaparinux (see later).

Contraindications: Warfarin, Platelet Transfusions, Vena Caval Filters

Warfarin

Warfarin is ineffective in acute HIT[6] and predisposes to microvascular thrombosis.[14,15] Venous limb gangrene is a more common manifestation of *coumarin necrosis* in HIT than is “classic” skin necrosis. In patients with acute HIT, it is recommended that warfarin be postponed pending substantial resolution of thrombocytopenia (preferably, platelet count $>150 \times 10^9$/L), with subsequent gradual initiation of warfarin anticoagulation.[10]

Administration of vitamin K is advised when acute HIT is diagnosed after warfarin has already been started:[10] besides reducing risk of coumarin necrosis, this might avoid underdosing of lepirudin and argatroban, since warfarin prolongs the activated partial thromboplastin time (APTT) used to monitor these anticoagulants.

Platelet Transfusions

Prophylactic platelet transfusions are *not* recommended, as petechiae and other evidence of impaired hemostasis usually are not seen in HIT, and transfused platelets might contribute to increased thrombotic risk.[10]

Vena Caval Filters

In my opinion, vena caval filters should be avoided, as their use in acute HIT often is complicated by massive lower-limb venous thrombosis. Further, the use of a filter might tempt physicians to avoid or minimize anticoagulation.

ALTERNATIVE NONHEPARIN ANTICOAGULANTS

Five alternative nonheparin anticoagulants have a rational basis for use in managing HIT.[10] Three (lepirudin, argatroban, bivalirudin) are direct thrombin inhibitors (DTIs), whereas two can be classified as indirect (antithrombin [AT]-dependent) inhibitors of activated factor X (Xa), either predominantly (danaparoid) or exclusively (fondaparinux). Lepirudin and argatroban are approved by the U.S. Food and Drug Administration (FDA) for treatment of HIT, whereas danaparoid is approved for this indication in Canada and Europe (but not in the United States).

Lepirudin (Refludan)

Lepirudin is a recombinant hirudin that forms irreversible 1 : 1 complexes with thrombin.[21] (Hirudin is the thrombin inhibitor produced by the medicinal leech.) This 65-amino acid polypeptide (6,980 Da) exhibits exceptionally high affinity for thrombin (Ki = 0.0001 nmol/L) resulting from bivalent binding, as it recognizes both the fibrin(ogen) binding site and a region near the active (catalytic) site of thrombin.[22] The half-life of hirudin (about 80 min) increases greatly in renal insufficiency. As no antidote exists, major dose reduction is required for renally compromised patients.

Lepirudin is FDA-approved for the treatment of HIT complicated by thrombosis. The approved dose (normal kidneys) is 0.4 mg/kg by i.v. bolus followed by an initial infusion rate at 0.15 mg/kg/h, adjusted for target APTT 1.5 to 2.5 times baseline. However, in the absence of severe thrombosis, and to reduce bleeding risk, it is advised to omit the initial bolus, to begin with a lower infusion rate (0.10 mg/kg/h), use a lower target APTT (1.5–2.0-times baseline), and monitor the APTT every four hours until steady state is established.[21]

Compared with historical controls, lepirudin treatment of HIT complicated by thrombosis was associated with reduced thrombotic events (relative risk reduction [RRR], 0.63–0.78).[12,17] Lepirudin also appeared effective for treating isolated HIT using a lower-dose protocol (0.10 mg/kg/h without initial bolus, adjusted by APTT).

Lepirudin’s foreign structure can trigger antihirudin antibodies that sometimes alter its pharmacokinetics, for example, drug accumulation resulting from impaired renal excretion of lepirudin-IgG complexes.[17,21] Thus, daily APTT monitoring is required. Fatal anaphylaxis following i.v. bolus administration has been reported.

Argatroban (Argatroban [U.S.], Novastan [non-U.S.])

Argatroban is a synthetic, small-molecule DTI derived from arginine (527 Da). It reversibly binds to the active site pocket of thrombin alone and thus is a univalent DTI. The Ki of argatroban for human thrombin is 40 nmol/L, indicating lower affinity for thrombin than hirudin [22]. Its half-life is 40 to 50 minutes, and it undergoes hepatobiliary excretion. Argatroban is FDA-approved for the prophylaxis or treatment of thrombosis in patients with HIT.

Argatroban is not immunogenic, and anaphylaxis has not been reported. The usual dose is 2 µg/kg/min adjusted by APTT (usual target, 1.5–3 times baseline APTT).[12,18] The starting dose should be reduced by 75% in a patient with significant liver dysfunction, or in a patient in the intensive care unit.

Compared with historical controls, argatroban was associated with reduced thrombotic events in treatment of HIT complicated by thrombosis (RRR, 0.44–0.62). The lower RRR compared with lepirudin could reflect the shorter mean treatment duration of argatroban therapy in its clinical evaluation compared with lepirudin (6–7 vs 13–14 days, respectively).[12]

Prolongation of the INR by argatroban is considerably greater than with lepirudin,[22] which can complicate argatroban–warfarin overlap; this underscores the importance of postponing warfarin pending substantial resolution of HIT. A recent study indicates that argatroban's greater effect on the INR results from its relatively low affinity for thrombin, and thus the need for greater molar concentrations (approximately 20-fold greater to double the APTT, compared with lepirudin). Thus, plasma concentrations of argatroban (~1.0 umol/L) are similar to the theoretical maximum amount of thrombin generated in the INR reaction.

Bivalirudin (Angiomax)

Bivalirudin is a 20-amino acid *hirulog* (analogue of hirudin) that unites a C-terminal segment of 12 amino acids (dodecapeptide) derived from hirudin to an active site-binding tetrapeptide sequence (D-Phe-Pro-Arg-Pro) at its N-terminus, bridged by four glycines (2,180 Da).[23] Indeed, bivalirudin connotes this bivalent binding to thrombin. Unlike hirudin, however, bivalirudin interaction with thrombin is transient, as plasma proteases cleave bivalirudin near its N-terminus. The affinity of bivalirudin for human thrombin (Ki = 2 nmol/L) is between that observed for lepirudin and argatroban; accordingly, its ability to prolong the INR is intermediate in comparison with these other two DTIs.[22] Like argatroban, bivalirudin is approved for use in a HIT patient who requires coronary angioplasty. Bivalirudin has undergone off-label use in HIT, particularly in the setting of off-pump and on-pump (cardiopulmonary bypass) cardiac surgery.[23]

Danaparoid (Orgaran)

This "heparinoid" (mixture of anticoagulant glycosaminoglycans) has both anti-Xa and anti-thrombin (anti-IIa) activity (anti-Xa/anti-IIa ratio = 22; 6,000 Da [mean]). It is available in Canada and Europe, but was withdrawn from the United States in 2002. It is effective for treatment and prevention of thrombosis in HIT, but its long half-life (25 h) and inability to inhibit clot-bound thrombin make it less than ideal for vascular surgery indications.

Both therapeutic- and prophylactic-dose regimens are available. For treatment of acute HIT (with or without thrombosis), the usual regimen is to administer an i.v. bolus (2,250 anti-Xa U, adjusted to 1,500 and 3,000 U for patients weighing <60 and >75 kg, respectively), followed by 400 U/h for four hours, then 300 U/h for four hours, then a continuous infusion of 200 U/h, with daily monitoring of anti-Xa levels (if available). The prophylactic-dose regimen is 750 U twice or thrice daily by s.c. injection, but patients with acute HIT should receive therapeutic doses even if thrombosis is not clinically apparent.[10] Thus, the low-dose regimen usually is given when clinical suspicion for HIT is not very high or if danaparoid is used in a nonacute HIT situation (e.g., antithrombotic prophylaxis in a patient with a previous history of HIT). The dose is usually reduced by about one-third in a patient with significant renal dysfunction. Although some HIT sera exhibit weak *in vitro* cross-reactivity with HIT antibodies, this is not predictive of adverse effects, and laboratory testing for cross-reactivity is not recommended.[10]

Fondaparinux (Arixtra)

This synthetic indirect (AT-dependent) inhibitor of factor Xa is modeled after the AT-binding pentasaccharide region of heparin (1,727 Da). Despite its small size (compared with natural heparin), prospective studies showed that anti-PF4/heparin antibodies are generated as often during fondaparinux therapy as with LMWH, although no patients developed thrombocytopenia.[24] However, the antibodies formed did not cross-react with PF4/fondaparinux, suggesting that fondaparinux might cause HIT even less often than LMWH (if at all), and perhaps might also be useful for treating patients with HIT (a situation for which LMWH is contraindicated). Since fondaparinux is FDA-approved for prevention and treatment of venous thromboembolism (2.5 mg and 7.5 mg once-daily by s.c. injection, respectively, for average-sized adults), it is appropriate for many patients with a previous history of HIT, in which repeat use of heparin usually is avoided.

Management of the Ischemic Limb

Evaluation of Limb Ischemia

The clinician must determine whether there is large and medium-size artery thrombosis that could be amenable to surgical thromboembolectomy, or whether limb ischemia reflects microvascular thrombosis, thus indicating a medical rather than surgical emergency (see Figure 44.2). Often, microvascular thrombosis is associated with proximal DVT in the same limb.

Arterial Thromboembolectomy

The vascular surgeon who manages a patient with limb-threatening ischemia due to artery occlusion in HIT faces the dilemma of how to anticoagulate such a patient during potentially limb-salvaging thromboembolectomy, as UFH is at least relatively, if not absolutely, contraindicated. There is anecdotal evidence that thrombi can recur during or soon

after thromboembolectomy if heparin is used, though this does not occur in all instances.

Section B of Table 44.4 lists various nonheparin options for intraoperative anticoagulation.[25] However, experience during vascular surgery with these approaches is minimal, and so risk-benefit considerations of any operative intervention must be judged individually. Whether monitoring is best performed using APTT, activated clotting time (ACT), or ecarin clotting time (ECT) is unresolved. Physicians should avoid "incidental" perioperative heparin exposure, for example, during preoperative angiography or intraoperative flushing of catheters.

Venous Limb Ischemia

Medical Management

Severe venous limb ischemia is a medical emergency, as effective anticoagulation may prevent its progression. Vitamin K (e.g., 10 mg i.v. over 30–60 min) is recommended for the patient who has received warfarin, or who has an elevated INR, since vitamin K antagonism or deficiency can explain venous limb ischemia.[10,14,15] The syndrome of *phlegmasia cerulea dolens* can be prodromal for venous gangrene, and prompt institution of effective anticoagulation can avoid critical limb ischemia.[14] Sometimes systemic or catheter-direct thrombolysis is given, but a caveat is that fibrin(ogen) degradation products produced by thrombolysis will bind and protect thrombin from its physiologic inhibitors, potentially worsening consumptive coagulopathy. Thus, in my opinion, at least moderate-dose anticoagulation should be given to a patient who is receiving thrombolysis (e.g., lepirudin, 0.10 mg/kg/h or danaparoid 100–200 U/h after an initial bolus).

Surgical Management

A surgical role for severe venous limb ischemia is less certain. Fasciotomy is sometimes performed in patients with suspected compartment syndrome, but this may delay or interrupt much-needed aggressive anticoagulation. Further, it is uncertain to what extent compartment syndromes contribute to limb ischemia in patients with HIT-associated DVT and associated microvascular thrombosis.

Preoperative and Postoperative Anticoagulation

A patient with HIT-associated thrombosis who requires intraoperative anticoagulation with a nonheparin anticoagulant may already be receiving this agent during the immediate preoperative period, thus obviating the need for a full intraoperative dose. There is also the dilemma of whether to continue the anticoagulant immediately postoperatively, or whether to suspend infusion until postoperative hemostasis appears secure. However, the prothrombotic nature of acute HIT suggests that continuing anticoagulation even during the immediate postoperative period (at least in low doses) can be appropriate.

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CHAPTER

45

Operative Venous Thrombectomy

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INTRODUCTION

Contemporary venous thrombectomy has the potential of offering patients with extensive iliofemoral and/or infrainguinal deep vein thrombosis (DVT) an opportunity for rapid resolution with significant reduction in postthrombotic morbidity. It is both surprising and disappointing that vascular surgeons in the United States have not moved beyond the criticisms of the venous thrombectomy procedure performed over 40 years ago. In the most recent ACCP consensus conference section addressing the management of patients with venous thromboembolic disease, it is stated that "in patients with DVT, we recommend *against* the use of venous thrombectomy (Grade 1C)."[1] They go on to say that "surgical thrombectomy is commonly complicated by a recurrence of thrombus formation." Unfortunately, the authors reference an anecdotal experience in patients treated over 40 years ago.[2] The follow-up on these patients was incomplete and biased. Only 50% of the patients originally treated underwent follow-up and only 25% had follow-up phlebography.

The early experience with venous thrombectomy was enthusiastically received because of reports of excellent patency without severe postthrombotic sequelae. Mahorner et al.[3] and Haller and Abrams[4] reported excellent patency rates in patients operated upon early for iliofemoral venous thrombosis. Haller and Abrams reported an 85% patency rate with 81% of survivors having normal legs without postthrombotic swelling. However, a subsequent follow-up report indicated higher rates of rethrombosis with failure to prevent postthrombotic sequelae, despite a patent deep venous system, presumably due to valvular incompetence.[2] This most damaging report was a five-year follow-up of patients originally described by Haller and Abrams. They reported that 94% of patients returning for follow-up had significant edema and skin changes, which required elastic stockings and leg elevation. Patients who underwent follow-up phlebography were found to have incompetent valves, although this represented only approximately 25% of the patients initially treated. Lansing and Davis[2] brought attention to the fact that two of the three postoperative deaths (in the 34 patients initially operated) were from pulmonary embolism (PE) and that there was a 30% wound complication rate, an average transfusion requirement of 1000 ml, and a mean hospital stay of 12 days. Critics of operative venous thrombectomy frequently fail to mention that the early technique was unlike modern thrombectomy procedures, with patients undergoing cut-downs on their iliac veins, femoral veins, and vena cava, often with flush and irrigation procedures performed to clear the venous system of thrombus, whereas venous thrombectomy today is performed with balloon catheters, and autotransfusion devices are available to minimize the need for blood transfusion. Completion phlebograms were essentially nonexistent with no effort to either identify or correct underlying venous pathology. Arteriovenous fistulae were not constructed and it is unclear to what degree patients were anticoagulated either during the procedure or postoperatively.

The report by Lansing and Davis suffered from a selection bias, since it is likely that the patients with the most severe postthrombotic sequelae were returning for follow-up and therefore the most heavily represented in their series. Furthermore, the patients reported represented only 50% of those initially operated upon, with phlebographic examination in far fewer. Another damaging report was that of Karp and Wylie,[5] who reported uniform rethrombosis following iliofemoral venous thrombectomy. Although the patients' clinical symptoms appeared to be improved, the

predischarge phlebographic documentation of rethrombosis led to further disinterest in venous thrombectomy.

Subsequent reports of successful thrombectomy from European centers,[6–13] with success rates reported as high as 88% without mortality, were for the most part ignored by surgeons in the United States. However, a number of vascular centers have persisted in using thrombectomy,[13,14] and with the ongoing experience and refinement of technique,[15] the results have markedly improved.

Most notable among these technical improvements are the use of a venous thrombectomy catheter (large balloon), fluoroscopic-guided thrombectomy with completion intraoperative phlebography, correction of an underlying venous stenosis, construction of an AVF, and immediate and prolonged therapeutic anticoagulation, often catheter-directed.

The ACCP consensus guideline authors failed to reference a contemporary randomized trial of venous thrombectomy and AVF versus anticoagulation alone in patients with iliofemoral venous thrombosis.[16–18] These patients underwent systematic follow-up with routine venous imaging and physiologic measurements. Peer-reviewed reporting occurred at six months,[16] five years,[17] and 10 years[18] of follow-up. Patients randomized to venous thrombectomy demonstrated improved patency ($P < 0.05$), lower venous pressures ($P < 0.05$), less leg swelling ($P < 0.05$), and fewer postthrombotic symptoms ($P < 0.05$) compared to anticoagulation.

RESULTS OF OPERATIVE VENOUS THROMBECTOMY

Although the early mortality rate in Haller and Abrams series was 9%, with two of the three fatalities attributed to PE, by the mid-1980s a progressive reduction in operative mortality was observed. Eklof and Juhan[19] reported their large experience in 230 patients undergoing venous thrombectomy for iliofemoral venous thrombosis. They reported no fatal PE and only one operative death. It is apparent that the application of venous thrombectomy now can be based on its effectiveness relative to competitive forms of therapy in reducing early morbidity and the late sequelae of iliofemoral venous thrombosis, rather than on the concern that the procedure will fail or be accompanied by complications.

Successful venous thrombectomy significantly reduces early morbidity in patients with phlegmasia cerulea dolens and phlegmasia alba dolens. The patients' pain and edema quickly subside and the discoloration resolves. The definition of benefit, however, may be masked by the additional cost of the operation, the need for blood transfusion, incisional discomfort, and wound complications. Interestingly, even if thrombectomy is not complete or is followed by some degree of rethrombosis, the limb rarely returns to its former morbid state if elevation and anticoagulation are continued. In our experience, thrombectomy has failed only when our own treatment guidelines were not observed. Although several patients may not have benefited, no patient has been made clinically worse, and we have yet to observe a symptomatic PE following the procedure.

TABLE 45.1 Venous Thrombectomy with Arteriovenous Fistula: Long-Term Iliac Vein Patency

Author/Year	No.	Follow-up (mos)	Patent iliac vein (%)
Plate et al. 1984[16]	31	6	76
Piquet et al. 1985[6]	57	39	80
Einarsson et al. 1986[7]	58	10	61
Vollmar 1986[8]	93	53	82
Juhan et al. 1999[9]	150	102	84
Torngren et al. 1988[10]	54	19	54
Rasmussen et al. 1990[11]	24	20	88
Eklof et al. 1996[13]	77	48	75
Neglen et al. 1991[12]	34	24	88
Meissner et al. 1996[25]	27	12	89
Pillny et al. 2003[26]	97	70	90
TOTAL	702	41 mos (mean)	78% (mean)

Adapted from Reference 29. Used with permission.

The long-term benefits of venous thrombectomy relate to its ability to achieve proximal patency and maintain distal valve competence. Both are influenced by initial technical success and the avoidance of recurrent thrombosis. Initial success in achieving patency is, in turn, influenced by timely intervention and attention to technical detail. Pooled data from a number of contemporary reports on iliofemoral venous thrombectomy (see Tables 45.1 and 45.2) have indicated that the early and long-term patency for the iliofemoral venous segment is in the 75 to 80% range compared with 30% patency in patients treated with anticoagulation alone,[20] and femoral-popliteal venous valve function is preserved in the majority of patients.

TECHNIQUE

The incremental goals that we believe are important for successful venous thrombectomy are summarized in Table 45.3. During the past two decades, the technique of venous thrombectomy has been refined and improved. Most of the principles of a successful procedure follow those established for patients undergoing arterial reconstruction for acute arterial occlusion. A number of important technical modifications have evolved, however, beginning with the accurate preoperative definition of the extent of thrombus (both proximally and distally) and whether the thrombus has embolized to the pulmonary vascular bed. The proximal extent of thrombus can be clearly defined by contralateral iliocavagraphy. It is especially important to determine

TABLE 45.2 Venous Thrombectomy with Arteriovenous Fistula: Long-Term Valve Competence of Femoropopliteal Venous Segment

Author/Year	No.	Follow-up (mos)	Femoral-popliteal valve competence
Plate et al. 1984[16]	31	6	52
Einarsson et al. 1986[7]	53	10	42
Ganger et al. 1989[27]	17	91	82
Neglen et al. 1991[12]	37	24	56
Kniemeyer et al. 1993[28]	37	55	80
Juhan et al. 1999[9]	150	60	80
Meissner et al. 1996[25]	27	60	30
TOTAL	352	45 mos (mean)	63% (mean)

From Reference 29. Used with permission.

TABLE 45.3 Technique of Contemporary Venous Thrombectomy

1. Identify etiology of extensive venous thromboembolic process
   a. Complete thrombophilia evaluation
   b. Rapid CT scan of chest, abdomen, and pelvis
2. Define full extent of thrombus
   a. Venous duplex examination
   b. Contralateral iliocavagram, MRV, or spiral CT
3. Prevent pulmonary embolism (numerous techniques)
   a. Anticoagulation
   b. Vena caval filter (if nonocclusive caval clot)
   c. Balloon occlusion of vena cava during thrombectomy
   d. Positive end-expiratory pressure during thrombectomy
4. Perform complete thrombectomy
   a. Iliofemoral (vena cava) thrombectomy
   b. Infrainguinal venous thrombectomy (if required)
5. Ensure unobstructed venous inflow to and outflow from thrombectomized iliofemoral venous system
   a. Infrainguinal venous thrombectomy (if required)
   b. Correct iliac vein stenosis (if present)
6. Prevent recurrent thrombosis
   a. Arteriovenous fistula
   b. Continuous therapeutic anticoagulation
   c. Catheter-directed postoperative anticoagulation (if infrainguinal venous thrombectomy is required)
   d. Extended oral anticoagulation

MRV, magnetic resonance venography; CT, computerized tomography.

whether thrombus has extended into the vena cava. Magnetic resonance venography with gadolinium or spiral computerized tomography (CT) scan with contrast may obviate the invasive procedure in some patients. Our preference is spiral CT scan with contrast, since a rapid CT scan of the chest can be performed simultaneously to evaluate for PE and other pathology, followed by a CT scan of the abdomen and pelvis, which not only localizes the proximal extent of thrombus, but also examines for intraabdominal and pelvic pathology.

During the operation, complete thrombus removal is ensured by completion phlebography. Correction of an underlying venous stenosis with balloon angioplasty and stenting (if needed) is critical to obtain unobstructed venous drainage into the vena cava. Residual iliac vein obstruction produces venous hypertension at best and often leads to recurrent venous thrombosis. Therefore, it must be identified and corrected. A properly constructed AVF increases venous velocity through the previously thrombosed iliofemoral venous system without increasing venous pressure, thereby decreasing the risk of rethrombosis. Prolonged therapeutic anticoagulation is important to prevent recurrence.

The more recent modifications, which include balloon catheter thrombectomy of the vena cava during suprarenal caval balloon occlusion for nonocclusive caval clot and infrainguinal venous thrombectomy followed by early and continued postoperative anticoagulation through a catheter remaining in the posterior tibial vein and construction of an AVF, are likely to further improve outcome. The sequential details of the contemporary venous thrombectomy are described in the following sections.

Preoperative Procedures

1. Evaluate the patient for an underlying thrombophilia. Since the majority of patients with DVT do not develop this degree of extensive thrombosis, the likelihood of identifying an underlying thrombophilia is high. If the patient is already anticoagulated, blood is sent for antiphospholipid antibody, factor V Leiden, prothrombin gene mutation, and homocysteine. These can be reliably performed in patients who are already being treated with heparin. A blood sample also is sent for type and cross-match.
2. Delineate the full extent of thrombus. It is always important to know whether the clot is involving the vena cava. A contralateral iliocavagram frequently is performed to assess the vena cava (see Figure 45.1). Additionally, a rapid spiral CT scan with contrast of the chest examines for PE as well as thoracic pathology. The subsequent abdominal and pelvic CT scans during the same contrast infusion can identify the proximal extent of thrombus and any intraabdominal or pelvic pathology that may be etiologically associated with the DVT (see Figure 45.2). We have found PE in approximately 50% of our patients. We have also found renal cell carcinoma with tumor thrombus extending into the vena cava, adrenal tumors, retroperitoneal lymphoma, hepatic metastases from unknown primaries, and iliac vein aneurysms. Each of these is critically important for proper patient management and would have been overlooked had the CT scan not been performed.

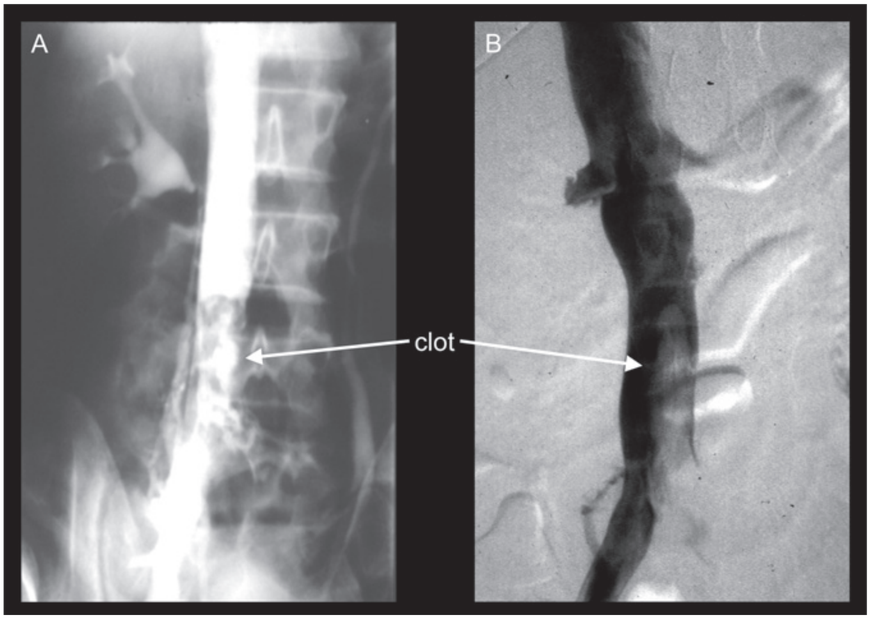

FIGURE 45.1 Contralateral iliocavagrams showing nonocclusive thrombus in the vena cava illustrate the value of imaging to detect proximal extent of thrombus.[29] Used with permission.

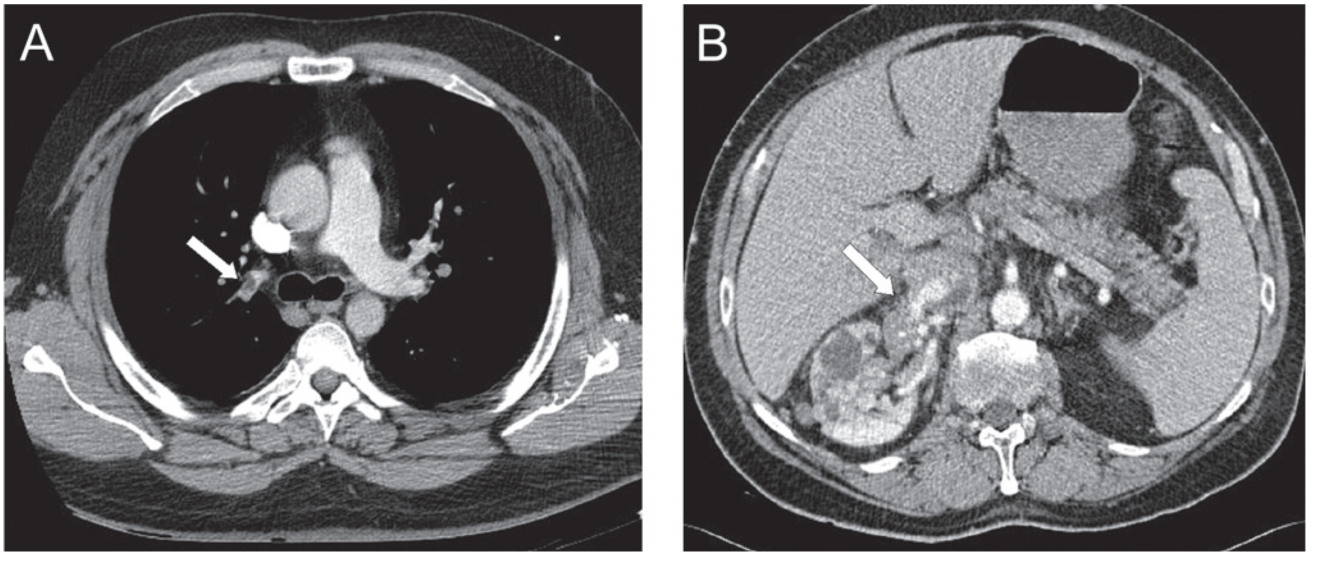

FIGURE 45.2 Asymptomatic PE (arrow, **A**) and renal cell carcinoma (arrow, **B**) identified with CT scan of chest as part of the evaluation of patients with iliofemoral DVT.[29] Used with permission.

3. Therapeutic anticoagulation with unfractionated heparin (UFH) is initiated after the blood samples are drawn for the thrombophilia evaluation. Unfractionated heparin is continued throughout the procedure and postoperatively.
4. Vena caval filtration is not routinely required. An exception may be those patients with nonocclusive thrombus extending into the vena cava (see Figure 45.1). The recently introduced optional (nonpermanent) vena caval filters have been used with plans for early retrieval. Patients with caval thrombus also have been managed with balloon occlusion of the proximal vena cava at the time of balloon catheter thrombectomy. The protective vena caval balloon is

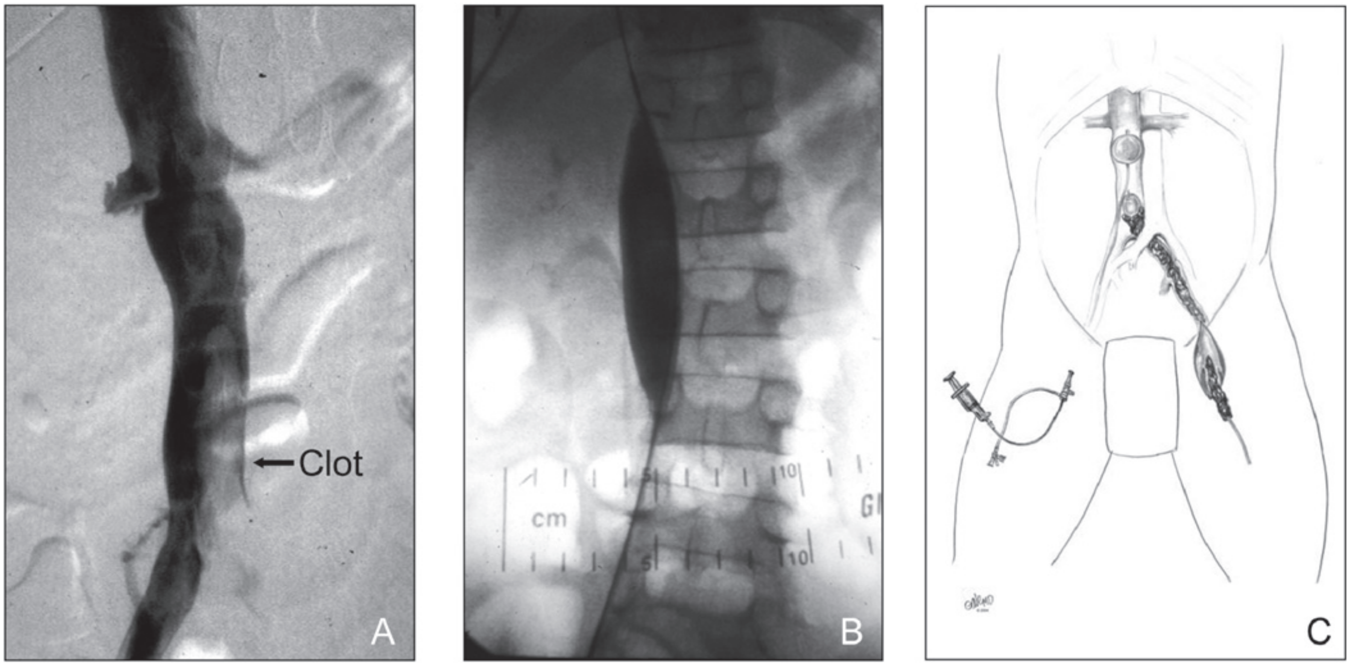

FIGURE 45.3 Preoperative iliocavagram shows nonocclusive thrombus extending from the left iliofemoral venous system into the vena cava (**A**). A suprarenal balloon catheter was placed from the contralateral femoral vein and inserted under fluoroscopy. The balloon is inflated at the time of thrombectomy (**B**). Schematic of iliocaval thrombectomy performed with the double balloon catheter technique, protecting the patient from pulmonary embolism (**C**).[15]

positioned during preoperative iliocavagraphy from the contralateral femoral vein using fluoroscopic guidance. After positioning, the balloon remains deflated until the time of thrombus extraction (see Figure 45.3).

5. The operating room is prepared for fluoroscopy. An autotransfusion device is made available during the procedure.

Operative Details

6. General anesthesia is recommended for the majority of patients.
7. A longitudinal inguinal incision is made with exposure and control of the common femoral vein, femoral vein, saphenofemoral junction, and profunda femoris vein (see Figure 45.4A).
8. A longitudinal venotomy is made in the common femoral vein at about the level of the saphenofemoral junction. The precise location of the venotomy depends upon the extent and location of the thrombus. Since the common femoral vein is dilated, closure of the longitudinal venotomy with fine monofilament suture can be achieved without compromising vein lumen.
9. The infrainguinal venous thrombectomy is performed first. The leg is elevated and compressed from the toes proximally with a tightly wrapped rubber bandage. The foot is dorsiflexed and the leg squeezed and milked to remove the clot from below.
10. If infrainguinal clot persists, a cut-down on the medial portion of the lower leg is performed to expose the posterior tibial vein in order to accomplish a balloon catheter infrainguinal venous thrombectomy (see Figure 45.4B). A #3 or #4 balloon catheter is passed proximally from below to exit from the common femoral venotomy (see Figure 45.5A). The stem of a plastic IV catheter (12–14 gauge) is slid halfway onto the balloon catheter coming up from below and another (#4) balloon catheter is placed into the opposite end of the plastic sheath. Pressure is applied to the two balloons to secure the catheters inside the sheath by a single operating surgeon. The #4 balloon catheter is guided distally through the venous valves and clotted veins (see Figure 45.5B) to the level of the posterior tibial venotomy (see Figure 45.5C). The infrainguinal venous thrombectomy is then performed with a #4 or #5 balloon catheter, if necessary (see Figure 45.5D,E), repeating catheter passage as required until no further thrombus is extracted.

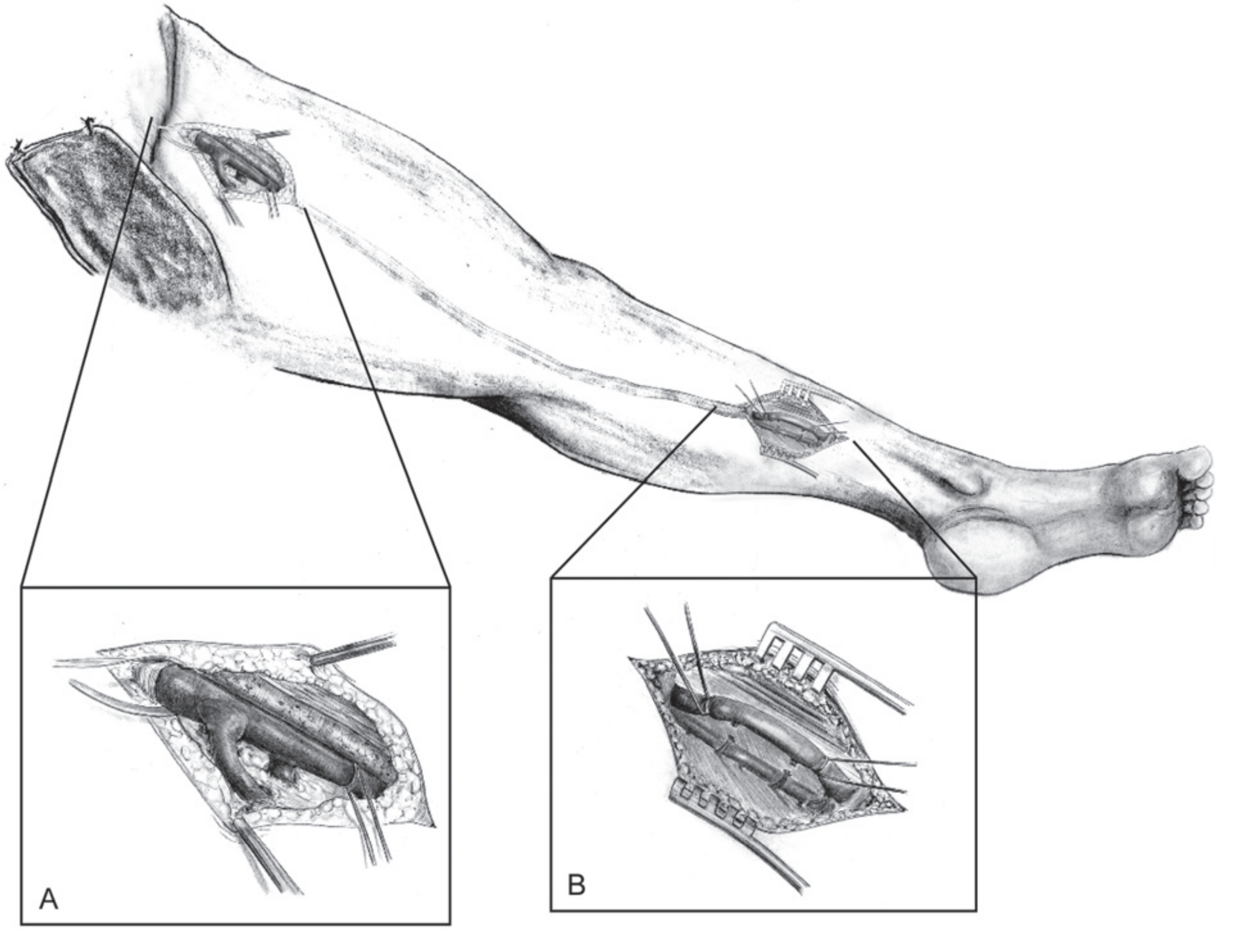

FIGURE 45.4 Exposure of the common femoral, femoral, and profunda femoris veins (**A**). Exposure of the posterior tibial vein (**B**).[30]

11. Following the infrainguinal balloon catheter thrombectomy, the infrainguinal venous system is vigorously flushed with a heparin-saline solution to hydraulically force residual thrombus (which can be considerable) from the deep venous system by placing a #14–#16 red rubber catheter into the proximal posterior tibial vein and flushing with a bulb syringe (see Figure 45.6). After applying a vascular clamp below the femoral venotomy, the infrainguinal venous system is then filled with a dilute plasminogen activator solution using approximately 4 to 6 mg of rt-PA in 200 cc of saline. The plasminogen activator solution remains in the infrainguinal veins for the remainder of the procedure. If the infrainguinal venous thrombectomy is not successful due to chronic thrombus in the femoral vein, the femoral vein is ligated and divided below the profunda. Patency of the profunda is ensured by direct thrombectomy, if required.
12. The proximal thrombectomy is performed by passing a #8 or #10 venous thrombectomy catheter partway into the iliac vein for several passes to remove thrombus before advancing the catheter into the vena cava. The proximal thrombectomy is performed under fluoroscopy with contrast in the balloon, especially if a vena caval filter is present, there is clot in the vena cava, or resistance to catheter passage is encountered. The anesthesiologist should apply positive end-expiratory pressure during the iliocaval thrombectomy. If there is clot in the vena cava, the caval thrombectomy can be performed with a protective balloon catheter inflated above the thrombus and the thrombectomy performed under fluoroscopy (see Figure 45.3).
13. After completion of the iliofemoral thrombectomy, the iliofemoral venous system is examined with intraoperative phlebography/fluoroscopy to ensure unobstructed venous drainage into the vena cava (see

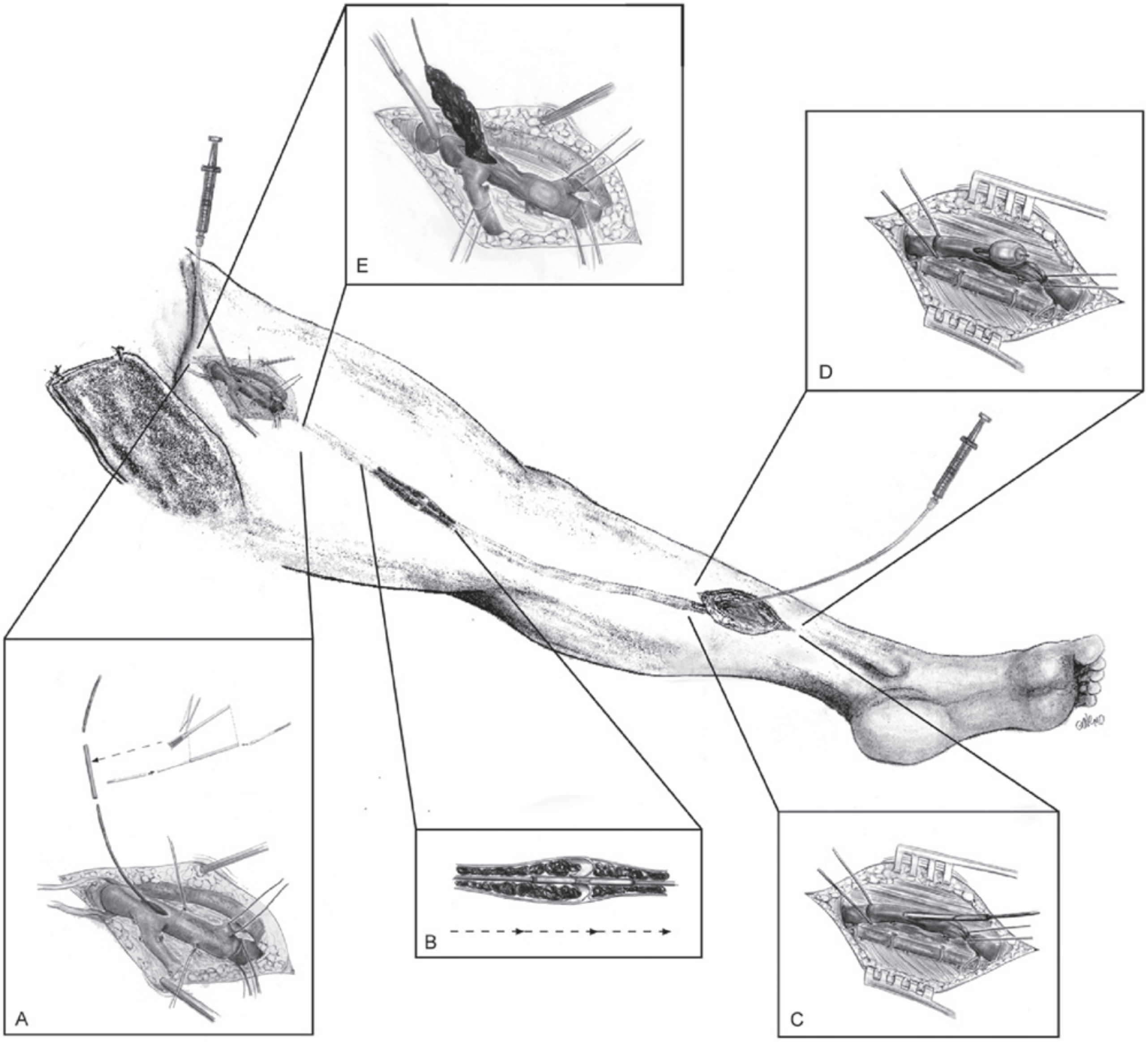

FIGURE 45.5 Technique of infrainguinal balloon catheter venous thrombectomy begins with passage of a #3 or #4 balloon catheter from the posterior tibial vein proximally, exiting the femoral venotomy. A silastic IV sheath is placed halfway onto the catheter and another #4 balloon catheter inserted into the other end of the sheath (**A**). The balloons are inflated to fix the catheter tips inside of the sheath with pressure applied by a single individual guiding them distally through the clotted veins and venous valves (**B**). Catheters and sheath exit the posterior tibial venotomy (**C**). The thrombectomy catheter balloon is inflated gently as the catheter is pulled proximally (**D**) to exit the femoral venotomy, extracting thrombus (**E**).[15]

Figure 45.7). Any underlying iliac vein stenosis is corrected with balloon angioplasty using a stent if venous recoil occurs. If a stent is used, a 12 mm diameter or greater is recommended.

14. After closing the venotomy with fine monofilament suture, an end-side AVF is constructed using the end of the proximal saphenous vein or a large proximal branch of the saphenous vein anastomosed to the side of the superficial femoral artery (see Figure 45.8A). The anastomosis should be limited to 3.5 to 4.0 mm in diameter. Frequently the proximal saphenous vein requires thrombectomy to restore patency prior to the AVF.
15. A piece of PTFE or silastic is placed around the saphenous AVF and a large permanent monofilament suture (#0) looped and clipped, leaving approximately

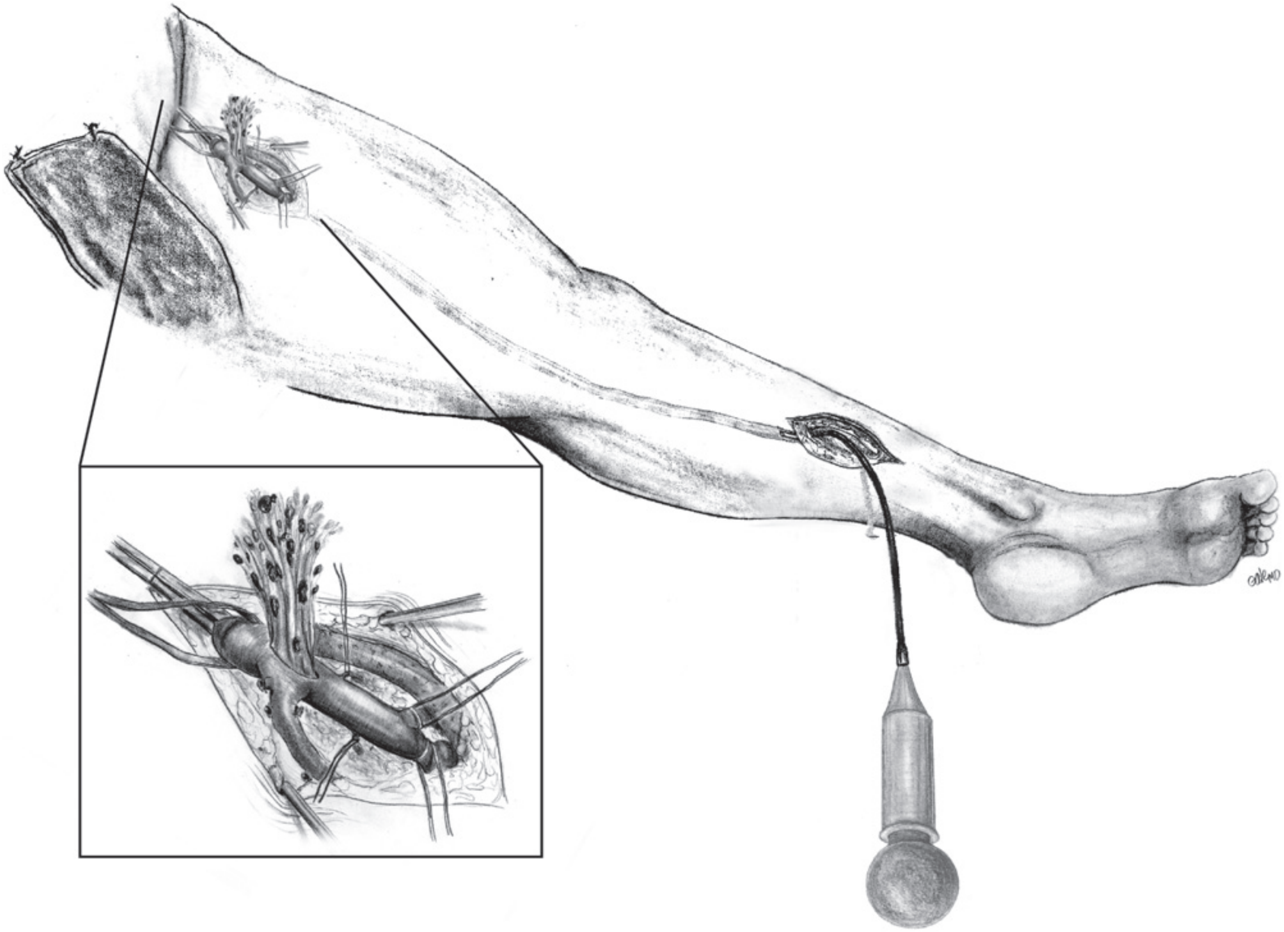

FIGURE 45.6 A red rubber catheter (largest diameter possible) is placed into the posterior tibial vein and vigorously injected with a heparin-saline solution using a bulb syringe to flush residual thrombus. After flushing, the femoral vein is clamped and the leg veins injected with 150–200 cc of a dilute UK or rt-PA solution.[15]

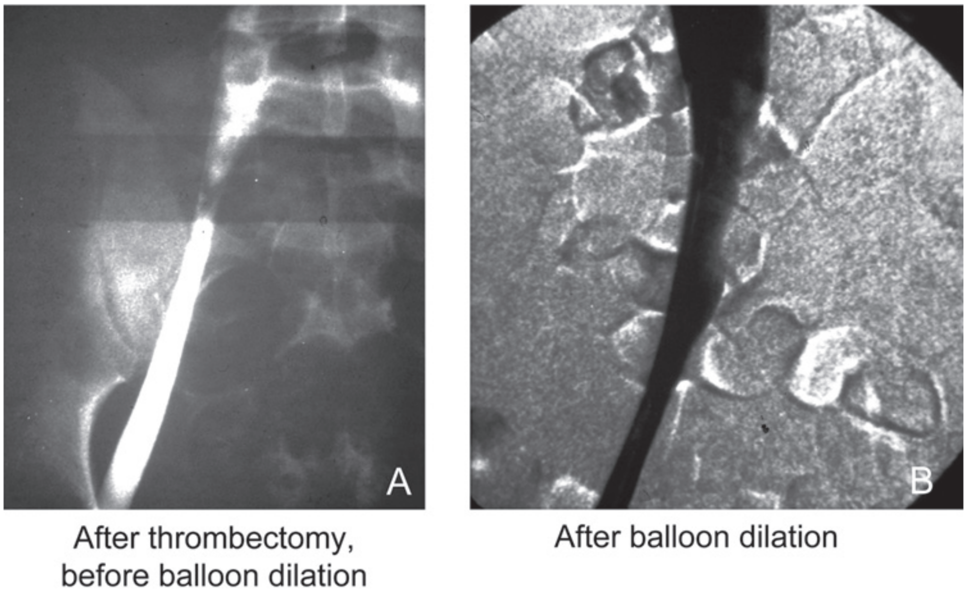

FIGURE 45.7 After thrombectomy, the right common iliac vein shows residual stenosis (**A**). Following iliac vein venoplasty, the stenosis is corrected, restoring unobstructed venous drainage into the vena cava (**B**).[29] Used with permission.

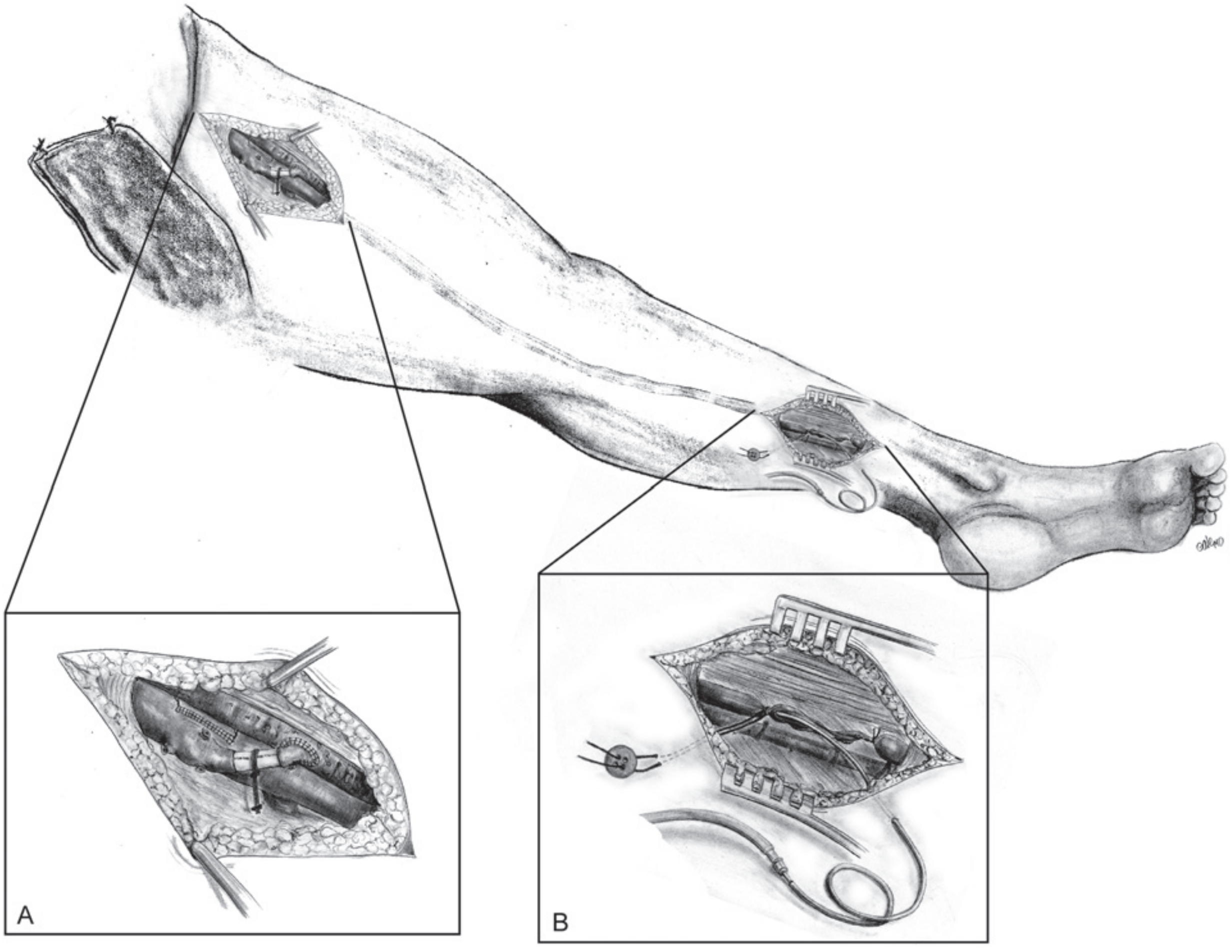

FIGURE 45.8 The venotomy is closed with fine monofilament suture, and a 3.5–4.0 mm AVF is constructed sewing the transected end of the saphenous vein to the side of the superficial femoral artery. A piece of PTFE (5 mm graft) or similar wrap is placed around the saphenous AVF, looped with #0 monofilament suture and the ends clipped, leaving approximately 2–2½ cm in the subcutaneous tissue to guide surgical closure of the AVF, should it be necessary (**A**). The distal posterior tibial vein is ligated. An infusion catheter (pediatric NG-tube) is brought into the wound through a separate stab wound in the skin and inserted and fixed in the proximal posterior tibial vein. The proximal posterior tibial vein and catheter is looped with #0 monofilament suture and fixed to the skin through a sterile button, which is used to snugly occlude the posterior tibial vein at the time of catheter removal (**B**).[15]

2 cm in the subcutaneous tissue (see Figure 45.8A). This will guide future dissection in the event that operative closure of the AVF becomes necessary; however, most do not.

16. The common femoral vein pressure is measured before and after the AVF is opened. The venous pressure should not change. If the venous pressure increases when the AVF is opened, the proximal iliac vein should be reevaluated for residual stenosis or obstruction, and the proximal lesion corrected. If the pressure remains elevated, the AVF is constricted to decrease flow and normalize pressure.
17. If there appears to be notable serous fluid in the wound, a search for transected lymphatics is performed and they are ligated or coagulated. A #7 Jackson-Pratt drain (or other similar closed suction drain) is placed in the wound to evacuate blood clot and serous fluid that may accumulate postoperatively. The drain exits through a separate puncture site adjacent to the incision. The wound is closed with multilayered running absorbable sutures to achieve a hemostatic and lymphostatic wound closure.
18. The distal posterior tibial vein is ligated. An infusion catheter (typically a pediatric NG tube) is brought into the wound via a separate stab incision in the skin and inserted and fixed in the proximal posterior tibial vein (see Figure 45.8b). This catheter is used for postoperative heparin anticoagulation and a follow-up

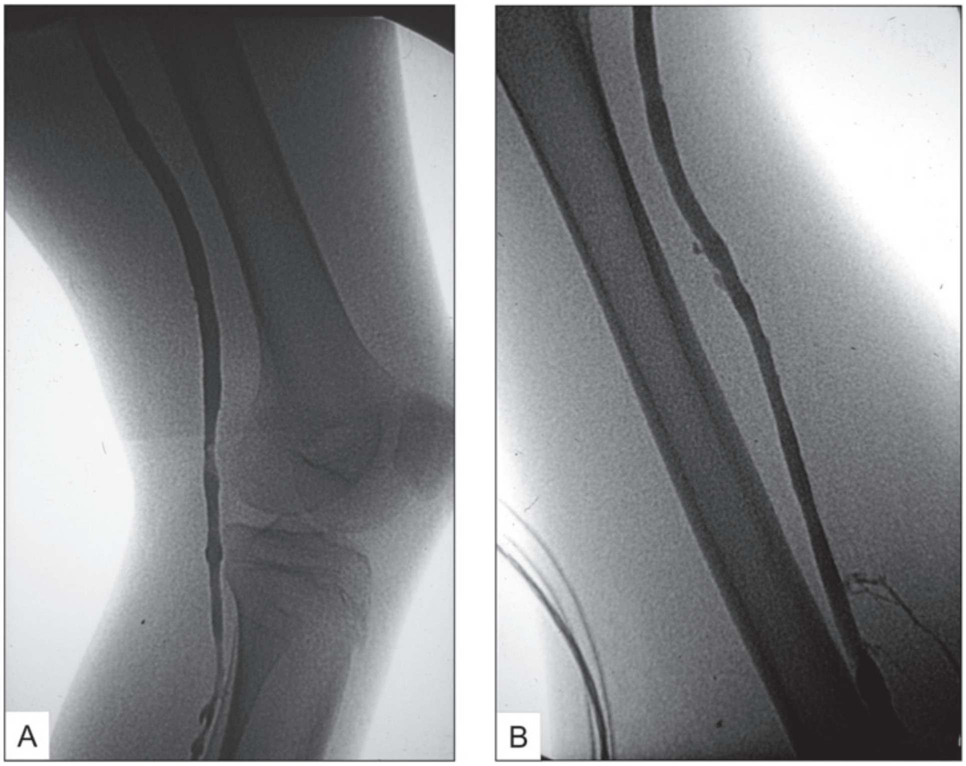

FIGURE 45.9 An ascending phlebogram evaluates venous patency prior to catheter removal, after the patient is therapeutic on warfarin.[30]

(predischarge) phlebogram. This ensures maximal heparin concentration into the affected venous segment. A 2-0 monofilament suture is looped around the posterior tibial vein (and catheter) and both ends exit the skin. The ends of the suture are passed through the holes of a sterile button, which is secured snugly to the skin when the catheter is removed. This obliterates the proximal posterior tibial vein and eliminates the risk of bleeding following catheter removal. Prior to catheter removal, an ascending phlebogram is performed through the catheter to once again examine the veins phlebographically (see Figure 45.9).

19. Antibiotic ointment and sterile dressings are placed on the wounds. The patient's leg is wrapped with sterile gauze and multilayered elastic bandages from the base of the toes to the groin. The bandages are snugly applied, with the posterior tibial vein catheter exiting between the layers of the bandage on the lower leg.

Postoperative Details

20. Full anticoagulation is continued postoperatively with UFH through the catheter in the posterior tibial vein. The heparin solution and pump are attached to an IV pole with wheels and the patient is allowed (encouraged) to ambulate. Oral anticoagulation is begun when the patient is awake and resumes oral intake. The heparin infusion is continued for a minimum of four to five days and the INR reaches 2–3.
21. Intermittent pneumatic compression garments are used on both legs during the postoperative period when the patient is not ambulating.
22. Prior to removing the posterior tibial vein catheter, a predischarge ascending phlebogram is obtained to evaluate patency of the femoropopliteal and iliofemoral venous segments. In the presence of an AVF, there may be significant washout of contrast in the common femoral vein, thereby mitigating good visualization of the iliac venous segments. Any significant stenosis in the iliofemoral venous segment should be treated to maintain unobstructed venous drainage into the vena cava.
23. Oral anticoagulation is continued for an extended period of time, at least one year in all patients and indefinitely in many.
24. Upon discharge the patient is prescribed 30 to 40 mmHg ankle gradient compression stockings and instructed to wear the stockings from the time he/she

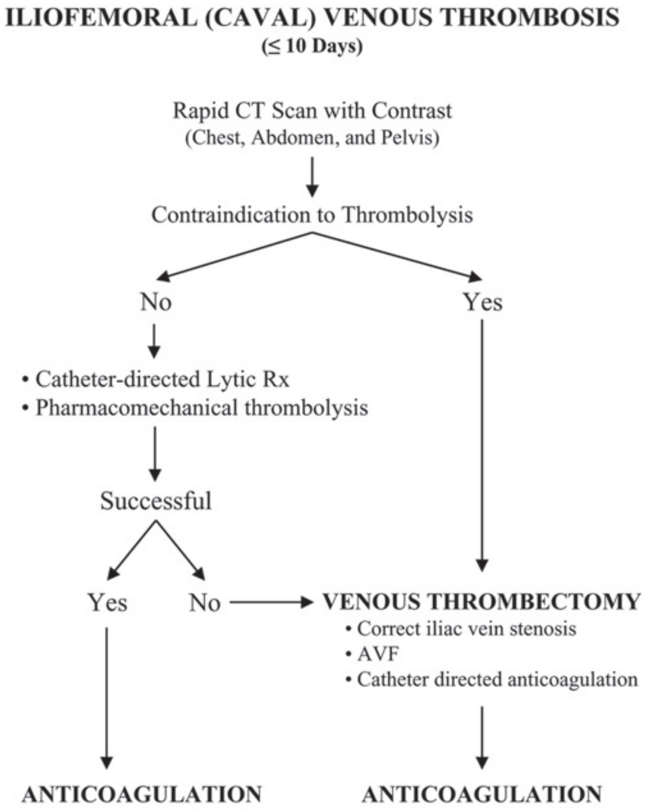

FIGURE 45.10 Algorithm: Recommended treatment for iliofemoral venous thrombosis.[30]

awakens in the morning until bedtime. Compression stockings further reduce postthrombotic sequelae.[21,22]

DISCUSSION

Based upon the available literature, patients with iliofemoral DVT routinely should be considered for a management strategy designed to remove thrombus from the iliofemoral system in order to reduce postthrombotic sequelae. Many patients are now treated as outpatients for acute DVT. However, when common femoral vein thrombosis with occlusion is identified by venous duplex, we would recommend that the patient be hospitalized and the strategy that is summarized in Figure 45.10 adopted. If the patient is not a candidate for catheter-directed thrombolysis, the recommendation for venous thrombectomy (Grade 1B) should be followed.

Successful thrombus removal results in improved quality of life and fewer postthrombotic sequelae.[16–18,23] A randomized trial of catheter-directed thrombolysis versus anticoagulation has shown better patency and preserved valve function in those treated with thrombolytic therapy.[24] Patients who have iliofemoral DVT and contraindications to lytic

TABLE 45.4 Venous Thrombectomy: Comparison of Old and Contemporary Techniques

Technique	Old	Contemporary
Pretreatment phlebography/CT scan	Occasionally	Always
Venous thrombectomy catheter	No	Yes
Operative fluoroscopy/phlebography	No	Yes
Correct iliac vein stenosis	No	Yes
Arteriovenous fistula	No	Yes
Infrainguinal thrombectomy	No	Yes
Full post op anticoagulation	Occasionally	Yes
Catheter-directed anticoagulation	No	Yes
IPC post op	No	Yes

IPC, intermittent pneumatic compression.
Adapted from Reference 29. Used with permission.

therapy should be considered for venous thrombectomy if they present within 10 days of the onset of their DVT.

Aggressive anticoagulation combined with leg compression[21,22] is the preferred treatment for patients who have a contraindication to thrombolysis, are poor operative candidates, have a prolonged duration of venous thrombosis, or are critically ill or bedridden.

Contemporary venous thrombectomy has substantially improved the early and long-term results of patients with extensive DVT compared to the initial reports. The major technical differences between the initial and contemporary procedures are listed in Table 45.4. Recent reports of those performing venous thrombectomy and the long-term results of a large Scandinavian randomized trial confirm significant benefit compared to anticoagulation alone. Therefore, vascular surgeons should include contemporary venous thrombectomy as part of their routine operative armamentarium.

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C H A P T E R

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Permanent Vena Cava Filters: Indications, Filter Types, and Results

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INTRODUCTION

The incidence of pulmonary embolism (PE) is estimated to be around 355,000 patients per year and results in as many as 240,000 deaths per year in the United States.[1] The standard treatment for PE remains therapeutic anticoagulation. However, 5 to 8% of patients receiving therapeutic anticoagulation for PE experience a second PE episode.[2,3] Complications of anticoagulation also occur in up to 26% of patients.[2,3] There are many instances in which anticoagulation is either contraindicated or patients experience a complication of anticoagulation necessitating its discontinuation. These instances include patients who are at risk for bleeding, for example, recent surgery or intracranial bleed, and patients who have recurrent PE despite therapeutic anticoagulation. In these situations, inferior vena cava (IVC) filter insertion is indicated to prevent PE.

HISTORICAL PERSPECTIVE OF CAVAL INTERRUPTION

Femoral vein ligation was first performed by John Hunter in 1874 and was advocated by Homans in 1934.[4] This technique caused frequent recurrent DVT and a PE. In the mid 1940s, Ochsner advocated IVC ligation to prevent emboli from the pelvis and legs.[5] However, this method was associated with a high mortality rate of 14%, a recurrent PE rate of 6% (2% fatal), and chronic venous stasis in 33% of patients.[6–9] Large collaterals were demonstrated after IVC ligation on venography, and these were thought to be a source for recurrent PE.[10] It was believed that the PE originated at the ligation site of the IVC.

The next stage of caval interruption consisted of compartmentalization of the IVC with sutures, staples, or clips (Moretz, Adams-DeWeese, and Miles clips).[11–13] IVC interruption using these techniques was associated with an operative mortality of 12%, recurrent PE rates of 4%, and IVC patency rate of 67%. These techniques also had the added morbidity of laparotomy and general anesthesia.

The next generation of caval interruption was the use of endovenous techniques. The Mobin-Uddin umbrella became the most popular because it can be done using local anesthesia under fluoroscopy.[14] It was constructed in the shape of an inverted umbrella from six stainless steel struts covered with a thin heparin-impregnated fenestrated silastic membrane.[14] The umbrella was inserted by venotomy with the apex pointing inferiorly. This device was withdrawn from the market because of a significant number of associated complications, including IVC thrombosis in 60% and migration in 0.4%.

In 1973, the Greenfield filter was introduced as the next generation of caval devices.[15] The outer diameter of the sheath of this filter is 29.5 Fr. The filter was inserted via venotomy with the filter apex cephalad. This filter could be filled to 70 to 80% of its length without flow alteration or pressure gradients. This filter also has the advantage of the paraxial flow around trapped thrombus, which could allow endogenous thrombolysis or fragmentation of the clot, thereby maintaining caval patency. This filter is traditionally the device by which other caval devices are compared, even though the original design is no longer commercially available.

The next generation of filters were the percutaneous caval devices, which began with the first percutaneous Greenfield filter in 1980.[16] Several lower profile percutaneously inserted caval filters have been developed since then, and, presently,

nine devices are approved by the U.S. Food and Drug Administration.

THE IDEAL CAVAL FILTER

Several ideal caval filter characteristics have been recognized.[17] These characteristics should include: 1) biocompatible, nonthrombogenic, with infinite implant lifetime performance; 2) secure fixation within the IVC; 3) high filtering efficiency with no impedance of flow; 4) small caliber delivery system with ease of percutaneous insertion with a simple and controlled release mechanism amenable to repositioning; 5) low access site thrombosis; 6) low cost; 7) retrievability; and 8) MR imaging compatibility. Many of these features have been achieved in some of the newer IVC devices, but the ideal device has yet to be developed. Long-term performance characteristics of caval filters are particularly significant in patients being considered for prophylactic IVC filter insertion.

INDICATION AND CONTRAINDICATIONS FOR CAVAL FILTER INSERTION

Table 46.1 summarizes the various absolute and relative indications for IVC filter insertion. This tables includes the established indications for caval filter placement and also summarizes indications that may be debatable or controversial.[18,19] Well-designed randomized prospective trials to determine the clinical role for caval filters are mostly lacking, although numerous case studies documenting the outcomes of widely used caval filters have been published. The large randomized study (PREPIC) assessing the value of caval filters compared with standard anticoagulation therapy was recently published.[20] This study included 400 patients with proximal lower extremity deep vein thrombosis and at risk for PE; 200 patients were randomized to a filter group and 200 were randomized to a nonfilter group. Both groups received standard anticoagulation. This study concluded that the beneficial effect of an IVC filter in PE prevention (1.1% versus 4.8% at day 12, p = 0.03) was outweighed by an excess of recurrent DVT (20.8% versus 11.6% at 2 years, p = 0.02), without a decrease in overall mortality. This conclusion stimulated intense criticism for multiple reasons:

1. The statistical power for comparing PE incidences at two years was extremely low because of a limited number of data points, which did not allow meaningful assessment of delayed PE rates.
2. In spite of the fact that overall mortality rates were similar, no deaths caused by PE were noted in the filter group, whereas 80% of the deaths in the nonfilter group were related to PE.
3. This study did not include a group of patients who received IVC filters without concomitant anticoagulation, which accounts for the majority of patients in clinical practice.
4. A higher rate of recurrent DVT did not outweigh the benefit of a decreased PE rate and reduced PE-related deaths because of greater gravity of recurrent PE in comparison with recurrent DVT.

Overall, patients with complications of anticoagulation or contraindications to anticoagulation should be managed with caval filter insertion alone. In certain patients, both caval filtration and anticoagulation may be used to protect these patients; for example, patients with chronic PE who are being considered for pulmonary embolectomy or patients with severe cardiopulmonary compromise that places them at greater risk if any additional embolic insults occur.

Relative indications for caval filters included the presence of iliofemoral thrombosis with a ≥5 cm free-floating tail. Although this indication has been questioned by a pro-

TABLE 46.1 Indications for IVC Filter Insertion

A. Absolute indications
1. Recurrent thromboembolic disease despite anticoagulation therapy.
2. Significant complication of anticoagulation therapy that forced therapy to be discontinued.
3. Uncontrolled anticoagulation: sub- or supratherapeutic despite patient compliance.
4. Recurrent PE in a patient with an IVC filter in place.
5. Contraindication to anticoagulation:
Bleeding complication of anticoagulation
Recent bleeding
Recent major trauma or surgery
Hemorrhagic stroke
Heparin-associated thrombocytopenia or thrombocytopenia (<50,000/mm^3)
Central nervous system neoplasm, aneurysms, or vascular malformation
Guaiac-positive stools
6. In conjunction with pulmonary embolectomy.
B. Relative indications
1. Large, free-floating iliofemoral thrombus.
2. Propagating iliofemoral thrombus despite adequate anticoagulation.
3. Thromboembolic disease with limited cardiopulmonary reserve.
4. Chronic thromboembolic disease (undergoing pulmonary embolectomy).
5. Poor compliance with medications.
6. Septic PE.
7. Severe ataxia; at risk for falls on anticoagulation therapy.
8. DVT thrombolysis.
9. Renal-cell cancer with renal vein or IVC involvement.
10. Prophylactic in high risk patients: massive trauma, pelvic, or lower extremity fractures, head injury.

spective trial,[21] thrombus with ≥5 cm free-floating tail may still be appropriately treated with caval filters. Other such indications are septic PE, chronic PE in patients with cor-pulmonale, high-risk patients including those with significant cardiopulmonary disease, occlusion of more than 50% of the pulmonary bed, or both, who could not tolerate any recurrent thromboembolism.

Several authorities suggested that the indications for filter insertions be made more liberal. These included patients who have sustained massive trauma and remain at high risk of thromboembolism, but do not actually have the disease.[22–24] Others have advocated the use of filters in patients with malignancy who are at risk for PE or who have thromboembolism.[25,26] The routine use of caval filtration for DVT instead of anticoagulation in high-risk older surgical patients and in pregnant patients with DVT or PE, have also been advocated.[27–29]

The increased liberal use of caval filters has been followed with the potential for unwarranted insertion. There are only sparse data on trends in the use of caval filters in patients with DVT alone, patients with PE, and patients at high risk. Stein et al.[30] analyzed the National Hospital Discharge Survey (NHDS) database for such trends. They used data from the NHDS, which is based on the national probability sample of discharges from short-stay nonfederal hospitals in 50 states and the District of Columbia. The numbers of sampled patients with PE, DVT, and IVC filters were determined from the International Classification of Diseases, 9th revision, clinical modification codes at discharge. The number of patients who had caval filters increased from 2000 in 1979 to 49,000 in 1999. Forty-five percent of caval filter insertions were in patients with DVT alone in 1999, 36% were in patients with PE, and 19% were in patients who were presumably at high risk, but did not have DVT or PE listed as a discharge code. The use of caval filters was more frequent in the northeastern states than in the western states ($p = 0.01$). They concluded that the use of IVC filters increased markedly during the last two decades in patients with PE, patients with DVT alone, and in patients at risk or with neither PE nor DVT.

The only known absolute contraindications to IVC filter insertion are complete thrombosis of the IVC and inability to gain access to the IVC. Replacement of IVC filters in younger patients (adolescent age) should also be avoided because of the lack of performance data lasting several decades. These patients would likely have such devices implanted for extended periods of time.

PROPHYLACTIC CAVAL FILTER INSERTION IN TRAUMA PATIENTS

Patients with multiple trauma have been considered for prophylactic caval filters. The usual prophylactic measures that are useful in the prevention of thromboembolic disease in surgical or medical patients, often fail in multiple trauma patients. Prophylaxis is often started too late in these trauma patients and there is frequent venous stasis and/or associated venous injury along with hypercoagulable states. Venous compression devices and venous surveillance ultrasound cannot be applied in many of these patients due to external fixation devices, the extent of edema, or the application of casts.

Although several reports have advocated the use of caval filters in high-risk trauma patients, other reports caution against routine prophylactic caval filter placement. In one large series, prophylactic caval filters would not have benefited 95% of high-risk patients without a DVT and would not have prevented any deaths.[31] These authors advised against prophylactic caval filters in high-risk trauma patients, with the exception of patients having major venous injuries. Most investigators have attempted to identify trauma patients at particularly high risk for thromboembolism and recommended prophylactic caval filter insertion.[32,33] These high-risk patients (e.g., brain or spinal cord injury, pelvic, and multiple long bone fractures) have been demonstrated to have a 50-fold increase in thromboembolic complications compared to other trauma patients. Most studies have demonstrated favorable outcomes with caval filters in such patients, however others failed to show this benefit.[23,32–35]

Wojcik et al.[36] reported on a series of 105 blunt trauma patients who were treated with permanent caval filters for treatment of DVT and prophylaxis, with a mean follow-up of 29 months. There was no PE in the patients in whom filters were placed, and no patients experienced any clinically significant complications related to caval filter insertions. They also reported minimal migration of only one filter and one caval occlusion (0.95%). However, 11 patients (10.4%) experienced symptoms of leg swelling after hospital discharge, and 28 of the 64 patients with prophylactically placed caval filters had a DVT after filter placement.

Rodriguez et al.[24] also reported on their experience of Greenfield filter insertion in trauma patients within 48 hours, with a PE related mortality decrease from 17 to 2.5%, and only two of 40 patients developed significant venous stasis of the lower extremities.

Leon et al.[37] reported on the prophylactic use of IVC filters in patients undergoing high-risk spinal surgery. Seventy-four spine surgery patients with contraindications to anticoagulation received prophylactic IVC filters with a mean age of 56 years. Criteria for usage were: 1) history of thromboembolism, 2) diagnosed thrombophilia, 3) malignancy, 4) bedridden for over two weeks prior to surgery, 5) staged procedures or multiple levels, 6) combined anterior/posterior approaches, 7) expected need for significant ilio-caval manipulation during exposure, and 8) single-stage anesthetic time over eight-hour period. Seventy patients had at least two risk factors. All patients received caval filters

prior to the first stage of spine reconstruction. Patients were evaluated for filter complications, DVT, and PE. Their lower extremity veins were also examined weekly until discharge using duplex ultrasound. One-third also underwent thoracic and pelvic computed tomography scans, and pelvic veins, IVC, and pulmonary vasculature were evaluated for venous thromboembolic events. At a mean follow-up of 11 months, one patient developed PE. Twenty-seven limbs in 23 patients developed DVT. Five limbs had isolated calf DVT, and 22 had proximal vein involvement. Insertion site DVT accounted for nearly one-third of the DVTs. Six patients died from unrelated complications. They concluded that despite the high incidence of DVT following high-risk spinal surgery, prophylactic caval filter placement appears to protect patients from PE.[37]

With the advances in the use of retrievable filters, the indication of prophylactic caval filters in trauma patients may be justified.

PROPHYLACTIC CAVAL INSERTION IN PATIENTS WITH MALIGNANCY

Patients with malignancies have hypercoagulable states and experience frequent thromboembolic events.[25,38] Some studies suggest that despite adequate anticoagulation, thromboembolism can occur in such patients to a greater degree than other patients. The associated comorbidities of patients with malignancies undergoing cancer therapy frequently places them at greater risk for bleeding complications from anticoagulation. The use of caval filters in these patients has been applied with conflicting results. In a recent report, the American College of Chest Physicians Consensus Committee on PE discouraged the routine use of IVC filters in cancer-associated DVT/PE and recommended the use of anticoagulation therapy until a randomized controlled study comparing the two modalities becomes available.[19] The use of filters has also been criticized in these patients due to the high cost and high mortality rate experience in these patients in many IVC filter studies.[25]

CAVAL FILTER INSERTION IN SEPTIC PATIENTS

The FDA guidelines for intravascular filters state that filters should not be implanted in patients with a risk of septic embolism.[39] Therefore, in septic patients who have a contraindication to anticoagulation, the physician must choose between placing the caval filter in contradiction to FDA guidelines and leaving the patient at increased risk of PE. However, this has been challenged recently. A review of a registry of 2600 patients in whom Greenfield filters were inserted over a 15-year period suggests that filter placement may be a safe method of PE prophylaxis in septic patients.[40] In reviewing 175 patients in this study with a diagnosis of sepsis at the time of caval filter placement, they noted an initial 33% mortality rate in this group; however, the mortality leveled out over time, suggesting the cause of death is related not to caval filter insertion but rather to the process of sepsis itself. No filters were removed from any patients, and the recurrent PE rate was 1.7%. Patients who underwent anticoagulation in addition to caval filter placement faired significantly better than those that did not. Thus, it appears that caval filter placement in septic patients receiving appropriate antibiotics, especially patients with contraindications to anticoagulation, may benefit from caval interruption. It should be noted that the employed filters in this study are made of titanium and stainless steel, both of which are inert materials.

CAVAL FILTER INSERTION DURING PREGNANCY

The choice of therapy for DVT of the lower extremity during pregnancy has been widely debated. Warfarin passes through the placenta to the fetus and may cause fetal complications and/or death. Heparin, in contrast, does not cross the placenta, but its long-term use may be impractical and may increase the risk of bleeding, osteoporosis, and neurological complications.

AbuRahma et al.[29] analyzed 18 pregnant patients who had Greenfield filters inserted for DVT of the lower extremity and/or PE. The DVT diagnosis was made using duplex imaging. Conventional full-dose intravenous heparin was initiated until the filter was inserted, followed by subcutaneous heparin until labor, and continued for six weeks postpartum in 13 patients who were breast-feeding. Warfarin was given postpartum in the other five patients. The mean age of these pregnant patients was 25 years. The indications for Greenfield insertion included three patients with PE while on anticoagulation, two with significant bleeding secondary to anticoagulation, four for free-floating iliofemoral DVT, two for heparin-induced thrombocytopenia, and seven with iliofemoropopliteal DVT occurring one to three weeks prior to labor, for prophylactic reasons. Fourteen of 18 cases were diagnosed in the third trimester. Filters were inserted via the right internal jugular vein by cutdown in the first four patients (stainless steel filters) and percutaneously in 14 patients. The mean fluoroscopy time during filter insertion was less than two minutes. There was no fetal or maternal morbidity or mortality. In long-term follow-up (mean: 78 months), no PE- or filter-related complications were encountered.

They concluded that Greenfield filter insertion in pregnant patients with DVT of the lower extremity is safe and effective, and its prophylactic use in pregnant patients who develop extensive iliofemoral DVT close to labor may be justified.

THE RESULTS OF IVC FILTER TRIALS

In a meta-analysis of IVC filters, Becker et al.[41] concluded that scientific evidence for filter effectiveness is lacking. The available data suggest that the risk of caval filter placement for prevention of recurrent PE is justified in the face of contraindications and failure of anticoagulation. Since caval filters are considered the standard of care in such instances, controlled trials for these indications may be unethical.[41]

Decousus et al.[20] reported the results of the first prospective study of caval filters in 1998. Four hundred patients with venography-proven DVT were randomly assigned to receive anticoagulant alone (heparin followed by oral anticoagulants for at least three months) or anticoagulants plus caval interruption with one of four different filters (the titanium Greenfield, Bird's Nest, VenaTech, and Cardil). The rate of recurrent venous thromboembolism (recurrent PE and/or DVT), death, and major bleeding were analyzed at 12 days and two years. The results demonstrated clearly for the first time in a randomized fashion that filters are effective in preventing PE. However, their efficacy was not accompanied by any improvement in overall mortality rates, mainly because fatal PE is actually quite rare. There was a significant two-fold increase in the risk of recurrent DVT within two years in the patient who had caval filters inserted. This study was criticized for several reasons.[42] This study originally was planned to include 800 patients (44 sites), but because of difficulty in enrollment, this study was stopped after only 400 patients had enrolled. The recurrent PE rate at two years suggested reduced rates for patients with filters, although there was no statistically significant difference between patients with filters and those without filters. The recurrent DVT rate in patients with filters did achieve significance at two years. It is possible that, if the entire patient population had enrolled, that recurrent PE rates at two years may have been significant. Because recurrent DVT is a more frequently expected event than recurrent PE, it is not surprising that it was easier to achieve a significant change in recurrent DVT. It should also be noted that the indications in which the caval filters were used also differs from the practice patterns commonly used, in which caval filters are used predominantly in patients in whom anticoagulation cannot be achieved.

Kazmers et al.[43] reported the results of a retrospective study at a VA Medical Center from 1990 to 1995 to define how caval filters affected in-hospital mortality rates. A total of 26,132 patients who had PE were included. The in-hospital mortality rate for those with PE was 15.9%. Only 157 caval filters were placed in patients with PE (3.2%). Those with PE who had caval filters inserted experienced a 13.4% unadjusted in-hospital mortality rate (21 of 157), versus 16% unadjusted mortality rate (754 of 4725) in patients treated without caval filters. However, the differences were not significant. In a logistic regression model of in-hospital mortality, the odds of death were reduced by 0.482 for patients with PE who underwent IVC filter insertion ($p < 0.05$). This study also showed across various centers, the use of caval filters for PE ranged from 0% to 16.7%. They concluded that caval filters were underused in veteran patients with PE.

In 2000, White et al. reported the results of a population-based study of the effectiveness of caval filters among patients with venous thromboembolism and concluded that insertion of filters was not associated with a significant reduction in the incidence of rehospitalization for PE.[44] This study evaluated hospital discharge data from California hospitals from 1991 to 1995 and was designed to determine the cumulative incidence at one year of rehospitalization for PE or venous thrombosis among patients with thromboembolism treated with caval filters compared with the incidence in a control population with thromboembolism not treated with filters. Three thousand six hundred and twenty-two patients were treated with filters and 64,333 control patients were admitted with a diagnosis of venous thromboembolism. Patients initially admitted with PE were significantly more likely to be readmitted for PE than patients with an initial episode of venous thrombosis only, among patients with caval filters (relative risk of 6.72) and control patients (relative risk of 5.3). Risk-adjusted proportional hazard models showed no significant difference between patients treated with filters and control patients in the relative hazard for readmission for PE. This study was limited because the patient treated with filters had significantly more comorbidities, a higher frequency of previous PE, and a lack of information regarding anticoagulation therapy. The authors concluded that patients with caval filters were at increased risk of caval occlusion because of accumulation of thrombus at the level of the filter, which was felt to be caused by clot accumulation during the time of recurrent thromboembolism.

In 2000, Athanasoulis et al.[45] reported a retrospective study with several different caval filters over a 26-year period. A total of 1765 filters were implanted in 1731 patients. A review of hospital records revealed a prevalence of PE after filter placement of 5.6%, with fatal PE occurring in 3.7% of patients. Major complications occurred in 0.3% of procedures and IVC thrombosis occurred after filter placement in 2.7%. They concluded that caval filters provided protection from life-threatening PE with minimum morbidity and a few complications.

TECHNICAL CONSIDERATIONS FOR IVC FILTER INSERTION

Caval filter insertion usually is performed under fluoroscopy, either in the operating room with C-arm fluoroscopy or in the radiology or endovascular suite where better imaging can be obtained. A preoperative venacavogram

should be obtained prior to filter insertion. The insertion of all currently available IVC filters requires venous access using the Seldinger technique. The introducer sheath is placed over a dilator, which is advanced over 0.035- to 0.038-inch guidewire. The filter is inserted into the sheath after the dilator and guidewire have been removed, placed in the proper position, usually below the level of the renal vein using an imaging technique, and deployed by unsheathing technique. In the majority of cases, the ideal level of placement is L2 or L3; however placement in the suprarenal IVC or superior vena cava may be indicated in some situations. The entrance site is usually the femoral vein (preferably, the right femoral) or the internal jugular vein.

The radiographic diameter of the IVC should be measured, with correction for magnification, which can be as much as 25%. A very large cava (above 30 mm in diameter) may be found in patients with right-sided heart failure. It may be safer to introduce separate filters into each iliac vein in these patients. Thrombus within the cava should not be allowed to contact the filter to prevent the propagation of thrombus through the filter. If thrombus does extend to the level of the renal vein, or the distal IVC is thrombosed, the filter should be placed at the level of T12 (suprarenal). After removal of the carrier system and the guidewire, a follow-up abdominal radiograph is obtained to confirm the position of the filter.

IVC Filter Placement at the Bedside Using Duplex Ultrasound Technique

With the advances in medical technology, most IVC filters are now placed percutaneously under fluoroscopic guidance in the angiography or endovascular suite. This technique has been very helpful in patients in the intensive care unit.[46–48] Bedside placement of IVC filters has several advantages, including minimizing the risk of contamination of central lines, and dislodgement of intravenous catheters during transfer from the ICU to the operating room or angiography suite. Many of these critically ill patients are on mechanical ventilation with continuous monitoring and/or on vasopressor support, which makes their move to other areas of the hospital rather difficult and hazardous. Many of these patients also have unstable pelvic fractures or spinal injuries. These patients can have their IVC filters inserted using a moveable fluoroscopy unit.

Recently, the use of transcutaneous duplex ultrasonography to visualize the IVC for placement of filters has been adapted in several centers.[46–48] This technique has several advantages, including the ability to perform the procedure at the bedside, particularly in the intensive care unit, avoiding the use of contrast material with its potential nephrotoxicity and ionizing radiation. The femoral veins, iliac veins, and the IVC usually can be visualized using duplex technology. Similarly, the internal jugular vein can be used as an access for the filter.

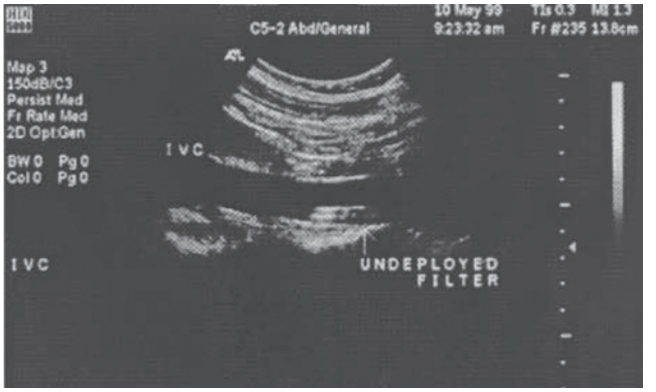

FIGURE 46.1 Undeployed filter within delivery catheter. Reprinted with permission.[48]

The patient generally is placed in the supine position for abdominal ultrasound examination. It is advisable for these patients to be NPO or to have their tube feedings discontinued for several hours to facilitate visualization of the IVC. The venous access via the femoral or internal jugular approach can be examined in the usual fashion. The vascular technologist generally is positioned opposite to the operating surgeon. An ultrasound transmission gel is applied to the abdomen. Once the IVC is identified and the renal veins are located, a long J guidewire is inserted into the venous access and can be visualized crossing the IVC. The delivery system, including the filter, is passed over the guidewire and can be visualized using the duplex ultrasound. Once the delivery system is properly positioned, the IVC filter can be deployed under direct vision. After inserting the IVC filter, the delivery system is then removed. A plain abdominal x-ray is then obtained to confirm the proper filter position (see Figures 46.1, 46.2, and 46.3).

Conners et al.[48] reported on 284 patients (out of 325 patients) who underwent duplex ultrasound-directed IVC filter placement. Poor IVC visualization, IVC thrombosis, and unsuitable anatomy prevented duplex-directed filter placement in 41 patients (12%). Indication for filter placement included venous prophylaxis in the absence of thromboembolism in 235 patients (83%), contraindication to anticoagulation therapy in 34 patients (12%), prophylaxis with therapeutic anticoagulation therapy in the presence of thromboembolism in seven patients (2%), and complication of anticoagulation therapy in eight patients (3%). There were no procedure-related deaths or septic complications. Technical complications occurred in 12 patients (4%). Filter misplacement occurred in six patients (2%), access thrombosis in one (<1%), migration in one (<1%), bleeding in one (<1%), and IVC occlusion in three (1%). Pulmonary emboli after IVC filter placement occurred in one patient with a

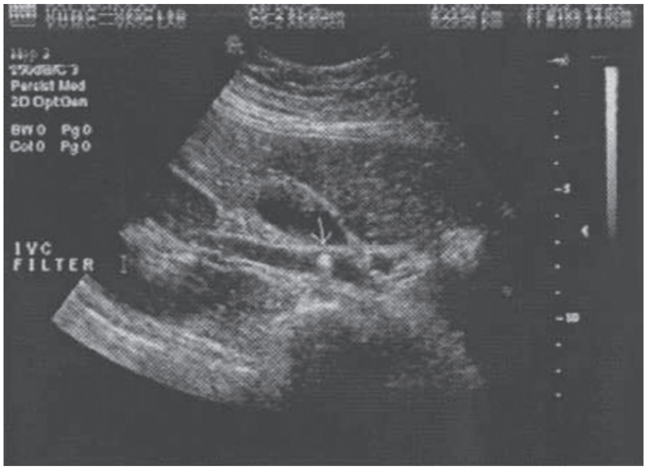

FIGURE 46.2 Greenfield filter tip (arrow) at right renal vein-inferior vena cava junction. Reprinted with permission.[48]

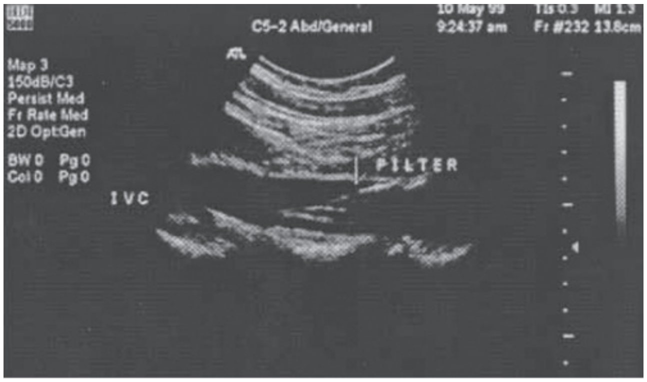

FIGURE 46.3 Filter deployed in inferior vena cava. Reprinted with permission.[48]

misplaced filter. Average hospital charges related to duplex ultrasound-directed filter placement were $2388 less than the fluoroscopic placement charges. They concluded that duplex ultrasound-directed IVC filter placement is safe, cost-effective, and convenient for patients who need IVC filter placement.

Corriere et al.[49] compared the results of bedside transabdominal duplex ultrasound versus contrast venography for IVC filter placement. A concurrent cohort of patients who underwent IVC filter placement at a single institution over a seven-year period with either contrast venography or transabdominal duplex ultrasound performed at bedside was retrospectively reviewed. Of 439 patients initially imaged with transabdominal duplex ultrasound, IVC filter placement was determined to be technically feasible in 382 patients (87%). The procedural technical success rate for IVC filter placement using transabdominal duplex ultrasound when IVC visualization was adequate was 97.4% (n = 382 patients) compared to 99.7% (n = 318 patients) for contrast venography ($p = 0.018$). Patients undergoing IVC filter placement with transabdominal duplex ultrasound more commonly required IVC filter for venous thromboembolism prophylaxis (81.1% vs. 27.8%, $p < 0.001$), had increased incidence of multiple traumatic injuries (28% vs. 10%, $p < 0.001$), and had increased risk from immobilization (91.3% vs. 34.1%, $p < 0.001$). Overall complication rates were 0.6% for venography and 1.8% for transabdominal duplex ultrasound (p = NS). When IVC visualization was adequate, contrast venography and transabdominal duplex ultrasound both had high rates of success and a low incidence of complications. A technical success advantage was observed for contrast venography; this difference in technical success must be weighed against the bedside insertion advantage offered by duplex ultrasound, which may be especially important in the immobilized or critically ill patient. They concluded that transabdominal duplex ultrasound remains their preferred technique when feasible, especially when bedside placement is desired.

Others have reported on the use of intravascular ultrasound for bedside insertion of IVC filters.[47,50–52] This technique has been described previously.[50]

Garrett et al.[51] analyzed the results of methods used to insert 256 IVC filters (207 with transabdominal duplex ultrasound [81%], 21 with fluoroscopy [8%], and 28 with IVUS [11%]). IVC filter placement with IVU was performed only if visualization with transabdominal duplex ultrasound was determined to be inadequate. Bedside IVC filter placement with IVUS was technically successful in 26 of 28 patients (93%). Post-procedure abdominal radiographs confirmed proper placement, based on bony landmarks in 24 of 26 patients (92%). Post-procedure complications included insertion site thrombosis in two patients and possible recurrent pulmonary embolism in one patient two months following filter placement. One patient died from causes unrelated to IVC filter placement. They concluded that IVC filter placement with IVUS is technically feasible and safe. This may allow for expanded bedside IVC filter placement capabilities in patients with inadequate IVC visualization on transabdominal duplex ultrasound.

OTHER IMAGING MODALITIES FOR IVC FILTER INSERTION

IVC filters traditionally have been inserted using conventional fluoroscopy, and more recently, transabdominal duplex ultrasound or intravascular ultrasound. Recently, other authorities have evaluated the role of other modalities in evaluating the IVC for filter placement. The use of iodinated contrast in critically ill trauma patients has been associated with the development of acute renal failure. The low incidence of nephrotoxicity associated with CO_2 makes it an ideal contrast for cavography. However, the use of CO_2

has been limited, because reportedly it underestimates the diameter of the IVC. Holtzman et al.[53] reported on the use of CO_2 cavagrams in 25 adult trauma patients requiring IVC filter placement. Bedside cavagrams using CO_2 followed by iodinated contrast were employed to determine the diameter of the IVC and the anatomy of the renal veins. Using CO_2 injection for cavography, they were able to determine the diameter of the IVC and the anatomy of the renal veins in all patients. Furthermore, when CO_2 cavography was compared with the results obtained with iodinated contrast, the difference in diameter of the IVC was within 1 mm. They concluded, based on these data, that CO_2 cavagrams can be safely performed in the intensive care unit during bedside placement of IVC filters.

Brown et al.[54] conducted a prospective study comparing gadolinium, CO_2, and iodinated contrast material for planning IVC filter placement. Forty patients underwent injection of iodinated contrast material, CO_2, and gadolinium. Iodinated contrast material was used as the standard. The measurements with CO_2 and gadolinium were compared to those with iodinated contrast material to obtain the interobserver and intraobserver variability. The presence or absence of caval thrombus and variant anatomy was noted. They concluded that CO_2 and gadolinium had limitations when compared with iodinated contrast material. Gadolinium provided superior consistency in identifying relevant landmarks for filter placement. CO_2 demonstrated significantly greater mean correlative error than gadolinium at initial and repeat readings.[54]

USE OF SUBCLAVIAN VEIN FOR INFERIOR VENA CAVA FILTER INSERTION

With the increasing use of central venous catheters and difficulty in venous access in some patient populations, alternatives to the traditional jugular and femoral vein approaches have been investigated. Davison et al.[55] reported successful placement of the TrapEase filter in five patients by using the antecubital vein. Ricco et al.[56] reported successful placement of LGM vena cava filters using the subclavian vein approach in eight patients.

Certain patient populations can pose challenges to using the standard routes of inferior vena cava (IVC) deployment. Trauma injuries can create difficulties in jugular access secondary to cervical immobilization, as well as limited exposure to access to femoral vessels secondary to lower extremity immobilization or fractures. Femoral vessel access may likewise be compromised in patients with iliofemoral DVT. In addition, some patients requiring IVC filters may also require long-term central venous catheter placement. Combined placement of both a vena cava filter and a subclavian long-term central catheter in these patients can provide a single expeditious procedure, especially if other access sites are compromised.

In 2004, we reported the results of 135 patients with TrapEase IVC filter placement over a two-year period. In a majority of cases, the choice of subclavian vein approach was based primarily on surgeon preference. Other circumstances for subclavian vein deployment included cervical immobilization secondary to trauma, desire for concomitant placement of a subclavian long-term central venous access catheter, and patient body habitus limiting exposure to the internal jugular vein. One hundred and thirty-five filters were placed over this two-year period. The internal jugular vein approach was used in 56 patients, the femoral vein approach in 39 patients, and the subclavian vein approach in 40 patients. Thirty-nine of the 40 TrapEase filter placements using the subclavian vein were successful. Twenty-six were deployed through the right subclavian vein and 14 through the left subclavian vein. The single failed subclavian deployment was due to the inability to pass the guidewire adequately into the inferior vena cava after successful cannulation of the right subclavian vein. The average deployment time for subclavian vein placement was 26 minutes when TrapEase filter placement was the only procedure performed. No insertional complications were encountered, specifically no pneumothoraces confirmed by chest radiography or fluoroscopy. We concluded that the subclavian vein provides an alternative site for access for the TrapEase IVC filter. This route is comparable to other alternative methods evaluated both in average deployment time and complication occurrence. Furthermore, the subclavian vein route is valuable in patients with limited central access and where combined long-term central venous catheter placement using the subclavian vein is desirable.[57]

SUPRARENAL IVC FILTER PLACEMENT

In certain clinical circumstances, suprarenal caval filter insertion is needed because it is impossible or inadvisable to place an IVC filter in the usual infrarenal location. Indications of these filters include: 1) patients with renal vein thrombosis, 2) infrarenal vena caval thrombosis, 3) requirement for IVC filtration in the presence of ovarian vein thrombosis in the postpartum state or the presence of a large patent left ovarian vein (pregnancy or child-bearing age), 4) the presence of thrombus propagating proximal to a filter below the renal veins, 5) extensive IVC thrombosis extending to or above the renal veins, including tumor thrombus from hepatic or renal tumors, 6) malposition or migration of a prior filter above the renal veins, and 7) recurrent PE following infrarenal IVC filter placement, preferably after an upper extremity emboli source has been ruled out.

Several studies have concluded that suprarenal IVC filter insertion is both safe and effective with clear indications for filter placement.[58–61] Overall, the efficacy and safety of Greenfield filters placed in a suprarenal position appear similar to that of filters placed infrarenally. A higher rate of

caudal migration was noted compared to infrarenal caval filters. The optimum choice for suprarenal IVC filters is, perhaps, either a titanium Greenfield filter or a wire-guided stainless steel Greenfield filter.

SUPERIOR VENA CAVA FILTER INSERTION

Several authorities have reported in small case series their experience with placement of filters in the superior vena cava.[62–66] These authorities felt that superior vena cava filters were beneficial in certain clinical indications, however others reported SVC thrombosis secondary to SVC filters.[66] Several studies have suggested that PE is not a rare complication of upper extremity DVT; however, it is believed that catheter-related upper extremity DVT can expose patients to a greater risk of PE. Indications for these filters would include contraindications to thrombolytic and anticoagulation therapy. The stainless steel Greenfield filter is generally believed to be an ideal choice for superior vena cava filtration because of its short length, alternating hook design, and being over the wire, allowing tracking and precise positioning. Guidewire entrapment may be more prone to occur with SVC filter placement.

FILTER PLACEMENT IN OVERSIZED IVCS

Oversized IVCs generally are defined as an IVC of more than 28 mm in diameter. The Bird's Nest filter is the device approved by the FDA for use in an oversized IVC. If this device is not available, insertion of bilateral common iliac vein filters is acceptable. It has also been noted that the titanium Greenfield filter and the new stainless steel Greenfield filter with alternating hooks may not be subject to the same 28 mm diameter IVC size limitation as the original Greenfield filter, with significantly better fixation in 34 mm diameter IVC. This is due to a wider base and redesigned hook pattern.

AVAILABLE CAVAL FILTER DEVICES

Stainless Steel Greenfield Filters

This filter is the gold standard to which all current and future filters should be compared. It is a stainless steel, cone-shaped filter 4.6 cm in length from the apex to the base. It consists of six legs that affix to the wall of the vena cava with small, recurved hooks.[67] The legs are 2 mm apart at the apex and 6 mm apart at the base when it is expanded in the vena cava (see Figure 46.4). It has the capability of catching emboli 3 mm or greater in diameter. Because the filter is cone-shaped, this allows the central portion of the cone or vena cava to become occluded by the thrombus or emboli while maintaining patency of the vena cava and filter around the circumference of the base. The functional capacity of the filter prevents progression of venous thrombosis, caval obstruction, and venous hypertension. For example, "when thrombus fills the filter to 70% of its depth, only 49% of the cross-sectional area is blocked. Experience has shown that no distal pressure increase occurs until 80% of the filter is filled with clot, at which point more than 64% of the cross-sectional area is blocked" (see Figure 46.5). It also has been noted that the centrally located trapped thrombi undergo breakdown with time due to continued blood flow around the perimeter. The filter is made of an inert metal and has been well-tolerated despite infection. Studies also have shown that entrapped thrombi that become infected can be sterilized with intravenous antibiotics. Due to its high patency rate, this filter has been placed above the renal veins in patients with thrombosis to the level of the renal veins. It has also been placed in the superior vena cava in rare circumstances. The filter originally was designed for placement by operative technique by way of the internal jugular or femoral veins.

The largest clinical experience was reported by Greenfield and Michna where 469 patients were followed for 12 years.[68] This study showed a long-term patency rate of 98%. The study also showed a failure to insert the filter in 0.6% of patients, misplacement of the filter in 2.5%, tilt of the filter in 1.7%, proximal migration in 0%, venous stasis in 5%, and a recurrent pulmonary embolism rate in 4%. Other studies confirm and support these findings.[69,70]

Similar results have been obtained in other follow-up series, with long-term patency rates in excess of 95%. The 20-year experience demonstrated the same low rate of recurrent PE and high rate of caval potency as seen in earlier reports.[71] This high level of patency has allowed placement of this filter above the renal veins when needed because of thrombus at that level or in pregnant women to avoid contact between the gravid uterus and the filter. The results of suprarenal filter placement are very comparable with 100% long-term patency rate in the 22 patients studied in the series of 69 filters placed at this level since 1976.[72,73]

The patency rate of Greenfield filters does not depend on prolonged anticoagulation and the termination of anticoagulant therapy is dictated by the underlying thrombotic disorders. This filter has also been reliable and has adapted to the needs of placement in the superior vena cava.

Titanium Greenfield Filters

The titanium Greenfield filter (Boston Scientific, MA; see Figure 46.4) is made of titanium alloy. Its cone shape is similar to that of the stainless steel Greenfield filter, but it is 8 mm wider at the base and 0.5 cm taller. It weighs 0.25 g as opposed to 0.56 g for the stainless steel Greenfield filter, and it can be compressed to a diameter of 0.144 inch.[67]

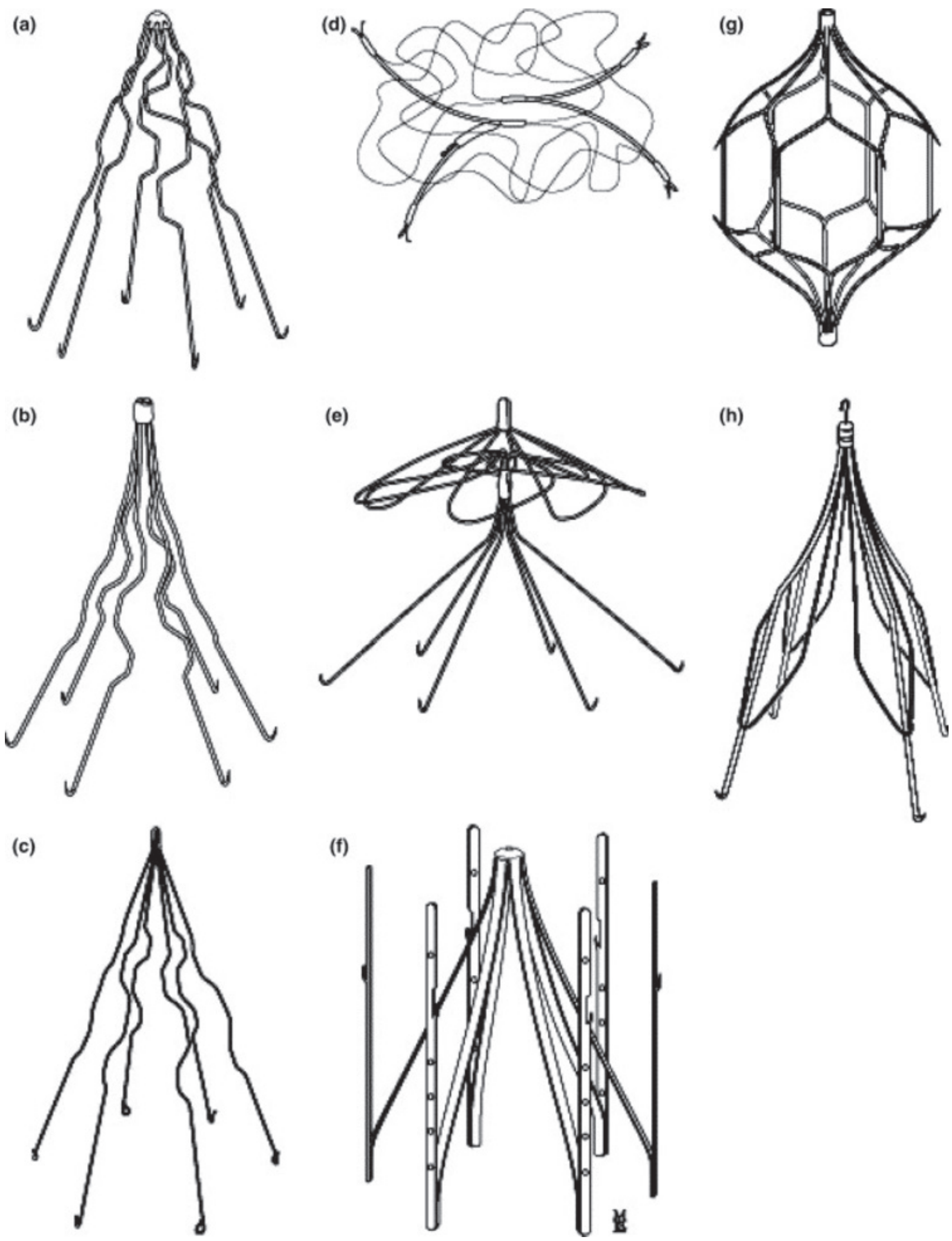

FIGURE 46.4 Vena caval filters: (a) Stainless steel Greenfield filter, (b) percutaneous stainless steel Greenfield filter, (c) titanium Greenfield filter, (d) Bird's Nest filter, (e) Simon Nitinol filter, (f) VenaTech filter, (g) Nitinol TrapEase filter, (h) Gunther Tulip filter (with permission). Reprinted with permission.[101]

Initial testing of the titanium filter showed distal slippage of the filter and less secure fixation to the wall of the vena cava. This was felt to be due to the filter's increased flexibility, which prompted a modification in the hook design. A recurved hook design with an 80 degree angle was selected. This hook design serves as a barrier to penetration beyond the axis of the limb and should limit both upward and downward vectors of force that might induce migration.[73] The mechanical properties of the titanium Greenfield filter have been tested extensively and it shows a remarkable resistance to flexion fatigue and induced corrosion. It exerts a force of fixation on the wall of the vena cava measurably greater than the stainless Greenfield filter at diameters over 22 mm, but less than the stainless Greenfield filter at diameters less than 22 mm. The titanium Greenfield filter requires a 12 Fr carrier system and an introducer sheath of 14 Fr. This reduction in size of the overall system has led to a reduction in insertion site venous thrombosis. Placement of the titanium Green-

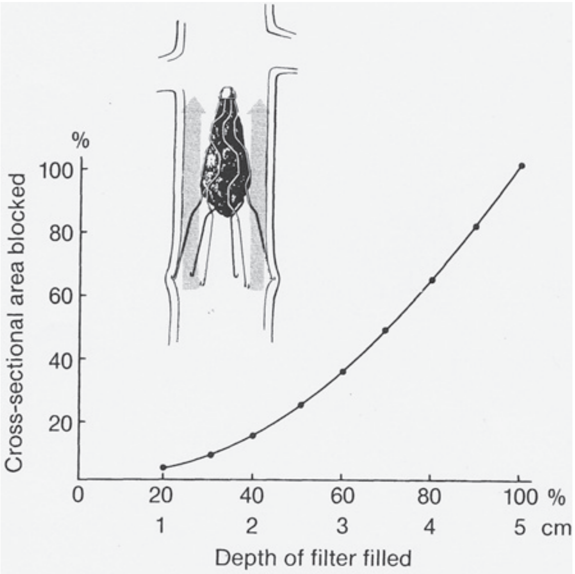

FIGURE 46.5 Relationship between the depth of filling of the Greenfield filter with thrombus and the obstruction to cross-sectional area. Even when 80% of the filter length is filled, less than 65% of the area is obstructed (with permission). Reprinted with permission.[73]

field filter requires a guidewire inserted percutaneously or by way of cutdown in the right jugular or femoral vein over which a dilator system and attached 14 Fr sheath are passed. When the dilator and sheath are in the IVC at the desired level, the dilator is removed. The titanium Greenfield filter carrier system is then placed through the sheath with fluoroscopic guidance. Both the sheath and carrier are retracted as a unit to release the filter. The carrier and sheath are removed and gentle pressure is applied to the insertion site to promote hemostasis. This design reduces premature misfire, which would place the filter in the sheath rather than in the patient. A new control handle that allows no manipulation other than retraction of the carrier for discharge of the filter decreases the risk of premature discharge. The filter is also preloaded into the carrier system that decreases the concern of crossed limbs.

The behavior of the titanium Greenfield filter seems comparable to the stainless steel Greenfield filter with increased corrosion resistance and tolerance to flexion stress. In addition, due to its decreased carrier size, both entry and positioning have been facilitated and bleeding during percutaneous filter insertion has been eliminated.

Experience with this filter has accumulated since the device was approved by the FDA in 1991. The initial prospective multicenter trial showed that filter insertion was successful in 181 out of 186 patients (97%): placement of the remainder was precluded only because of unfavorable anatomy.[74] All but two of the insertions were performed percutaneously. Leg asymmetry was seen in 5%, and there was no association between this asymmetry and either recurrent PE or penetration of the wall of the IVC. Filter apex perforation of the IVC at the time of insertion occurred in one patient after introduction from the left groin, and there was misplacement of one filter into a lumbar vein in another patient, with no clinical sequelae in either patient. Initial follow-up data, obtained from all participating centers at 30 days, showed minimal filter movement in 11%, with no significant proximal migration. There was evidence of penetration of the wall of the IVC in only one case (0.8%), with no clinical sequelae. In another clinical study of the titanium Greenfield filter the follow-up period was extended to at least 12 months. The late patency rate was 99%, with recurrent PE in 3.7% of 176 patients who were enrolled in this study.[75]

Stainless Steel Over-the-Wire Greenfield Filter

This is a 12 Fr stainless steel filter (Boston Scientific, MA) that is used as an alternative device for percutaneous placement (see Figure 46.4). This device allows for over-the-wire delivery and a flexible carrier system to facilitate safe delivery. It is the tallest of the Greenfield filters, at 4.9 cm, with a resting base diameter of 3.2 cm, between those of the titanium Greenfield filter (3.8 cm) and the original Greenfield filter (3.0 cm). Two of the six hooks of this filter are angled distally (see Figure 46.4), which facilitates secure fixation within the vena cava. The device is manufactured from the same material as the original stainless steel Greenfield filter, but the wires exit from the apex at a different angle, which facilitates delivery via a 12 Fr system. The results of clinical trials of this filter have demonstrated comparable results to the 24 Fr and titanium filters with respect to efficacy (95%) and patency (95%).[76]

Bird's Nest Filter

The use of the Bird's Nest filter (Cook, Bloomington, IN) was first reported in 1984,[77] and a large series of 568 patients was reported in 1988.[78] The device consists of four stainless steel wires 25 cm long and 0.18 in diameter. The wires are preshaped into a criss-crossing, nonmatching array of bends intended to provide multiple barriers to thromboemboli (see Figure 46.4). The end of each wire is attached to a strut that ends in a hook for fixation to the wall of the vena cava.[77,78] One strut is z-shaped so that a pusher wire can be attached for insertion. The initial filter was preloaded into an 8 Fr Teflon catheter, but this was associated with a high rate of proximal migration. The filter was redesigned in 1986 using a stiffer 0.46 mm wire to improve fixation. Modification of the filter resulted in an increase in the

preload system to a 12 Fr size. During insertion of the filter, the pusher is used to set the first group of hooks into the caval wall. The wires are then extruded with the goal of closely packing the formed loops into a 7 cm segment of the infrarenal vena cava. The second group of hooks are then pushed into the wall of the cava, and the pusher is removed by unscrewing it from the filter. The theoretic advantages of this filter include: 1) the ability to trap small emboli by virtue of the righter meshing of wires; 2) the ability to accommodate cavae as large as 40 mm in diameter; 3) the possibility that wires may be able to occlude nearby collaterals; 4) avoidance of the need for intraluminal centering because of the configuration of the device; and 5) the lack of radically oriented struts, thereby limiting the tendency toward caval wall penetration.[73] Only 37 of 481 patients with the filter in place for more than six months were available to follow up. Seven (19%) patients had occlusion of the vena cava, three symptomatic patients had pulmonary angiography for recurrent thromboembolism that was confirmed in one (3%), and proximal migration was seen in five patients resulting in one death secondary to the filter being embedded in a massive pulmonary embolus.[73] These results occurred before strut modification. In a study of the new modified strut, there were three cases of filter migration in 32 placements.[79] Two of these were identified within 24 hours of placement and were corrected by angiographic manipulation. The third was not detected until six months after placement, and it was embedded in the right atrium and ventricle and could not be repositioned.

More recently, Nicholson et al.[80] reported on the long-term clinical follow-up of the Bird's Nest filters in a small group of patients. Seventy-eight consecutive patients with filter placed between 1989 and 1994 were recalled for clinical assessment and imaging studies, including abdominal radiography, color duplex ultrasound, and CT of the abdomen in 52 patients that were still alive at the time of the study. Recurrent PE occurred in 1.3% of patients, and IVC occlusion in 4.7%. There was no filter migration. Wire prolapse was visualized in 70% by abdominal plain film. CT also showed asymptomatic penetration of the IVC wall in 85.3% of the patients studied. Aortic penetration was also reported, resulting in a clinically significant aortic pseudoaneurysm from penetration of one of the filter struts, which required repair.[81] The rate of IVC occlusion associated with the bird's nest device appears to be similar to other caval devices, although estimates range from 0% to 19%.[77,82] Lord et al.[82] reported the results of a retrospective study of 140 patients with Bird's Nest filters. Ninety-three patients were contacted, seven of whom (7%) were found to have caval thrombosis, five with duplex scanning, two on the basis of clinical symptoms despite anticoagulation. Results of these studies show the rate of IVC thrombosis to be comparable to other filters, but somewhat slightly higher than the rate of the Greenfield filters.

Simon Nitinol Filter

The nitinol filter (Bard, Covington, GA), first described in 1977, is made of a nickel-titanium alloy and is a pliable straight wire when cool, but transforms rapidly into a previously imprinted, rigid shape when warmed. The filter is a 28 mm dome shape with eight overlapping loops below which the wires are shaped into a cone with six diverging legs with terminal hooks, used to affix it to the vena cava wall (see Figure 46.4).[83] The filter wire is advanced rapidly with a feeder pump using iced, normal saline infused through a 9 Fr delivery catheter. When it is discharged from the storage tube, it expands instantly, assumes the appropriate shape, and is locked into place (see Figure 46.4).

Of 103 patients undergoing placement at 17 centers, only 44 were available for follow-up.[83] There were three cases of recurrent pulmonary embolism, seven cases of confirmed vena cava occlusion, and two suspected cases based on clinical examination. Five of 18 patients studied by ultrasound showed insertion site thrombosis. Of the 44 patients followed, 10 were studied at three months, but only four completed a six-month follow-up. Of these patients, six occlusions of the vena cava were documented and two additional occlusions were suspected, for an occlusion rate of 18%. Five patients developed edema with signs of filter thrombus, two developed recurrent embolism, and one filter migration was seen. In a more recent study of 224 patients, 65 (29%) patients completed a six-month follow-up.[84] Four percent of patients developed recurrent pulmonary embolism, one being fatal; 19.6% had caval occlusion; and three deaths were associated with massive caval thrombosis. It is currently believed that the nitinol filter may be thrombogenic.[84]

In 1998, Poletti et al.[85] reported on the long-term performance of Simon nitinol filters in 114 consecutive patients with an average follow-up of 27 months after placement. They prospectively evaluated 38 of these patients with previously placed filters by means of abdominal x-rays, duplex scanning, and abdominal CT scanning. The remaining patients were retrospectively evaluated from follow-up clinical data. Five patients (4.4.%) had recurrent PE and 5.3% had documented DVT with thrombosis at the exit site noted in 3.5%. Filter migration was not found in this series, but IVC thrombosis was noted in 3.5%. The nitinol filter was found to have penetrated the IVC wall in 95% of patients and was found to be in contact with adjacent organs in 76%; however, all of these were asymptomatic. Sixty-three percent of the filters were eccentrically positioned within the vena cava, and 16% were found to have partial disruption that did not appear to affect filter function. In 2001, Wolfe et al.[86] reported a recurrent PE rate of 7.7% with evidence of IVC penetration in all 117 patients they analyzed. Strut fracture was noted in 2.9% of patients, and

19% had eccentrically oriented filters. They also reported no cases of IVC thrombosis in their study.

VenaTech Filter

The VenaTech filter (B. Braun, Boulogne, France) was first introduced in France in 1986. It is a cone-shaped filter with added stabilizing struts on each limb designed for percutaneous use. The filter is made of phynox and is a stamped, six-prong device with hooked stabilizers with sharp ends intended to center and affix the device (see Figure 46.4).[67] The filter uses a 12 Fr catheter system usually inserted through the right internal jugular vein over a guidewire.

The early experience from France shows 100 attempts at insertion, resulting in 98 filter discharges. Eighty-two filters were in the correct position, eight showed a tilt of 15 degrees or greater, and eight had opened incompletely, with three of these associated with a tilt.[87] A more recent report showed a 2% recurrent embolism rate, a 23% rate of insertion site venous thrombosis, a 6% rate of filter patency without thrombosis, a 14% migration rate, and a 6% rate of incomplete opening.[88] Breakage of the stabilizer struts also has been reported.[4] This filter was designed to prevent tilt, but continues to show a high incidence of tilting.

A late experience with this filter showed an occlusion rate of 22%.[89] Long-term studies of this device by Crochet et al.[90,91] have demonstrated that there has been a 73% incidence of filter occlusion over time. Crochet et al.[91] prospectively evaluated 142 patients by means of follow-up every two years, using plain abdominal x-ray, IVC duplex ultrasound, venography, or a combination of these studies. They noted a progressive decrease in IVC patency rates, which reached 66.8% at nine years of follow-up, that is, a filter patency rate of 35.2%. Complete occlusion occurred in 28 patients, which were significantly associated with retraction of the filter in 24 cases and was associated with a lack of anticoagulation. They also noted that patients who received anticoagulation had an 80% patency rate during the same time period.

VenaTech Low Profile Filter

The VenaTech low profile (VenaTech LP) is a new filter with a release wire design contained within a 6 Fr introducer sheath, allowing placement of the filter through alternative venous access sites. This filter is 43 mm in height and 40 mm in diameter in an unconstrained state. This filter was approved in 2001 by the FDA for placement of IVC filters that were 28 mm or less in diameter, but may eventually be approved for vena cavas as large as 35 mm.[92]

Gunther Tulip Filter

The Gunther Tulip filter (Cook, Inc.) is a low-profile filter that uses the same funnel-shaped design as the Greenfield filter (see Figure 46.4). This filter was introduced in 1992 for use in Europe and has been available in the United States since 2001. The filter is constructed from elgiloy, an MR imaging-compatible material. It consists of four main struts, each 0.45 mm in diameter, configured as a cross. Each strut has an elongated wire loop that extends inferiorly three-fourths of the length from the apex to the hooked end of the four main cross struts. The four main struts contain 1 mm long hooks at the inferior end for caval fixation. The filter is 30 mm in diameter and 45 mm long in its fully expanded state. The filter can be placed using 8.5 Fr introducer sheaths via the femoral or jugular vein.

Most of the clinical applications of this filter have been as a retrievable filter. This filter is FDA approved for permanent implantation. Although the Gunther Tulip filter is used as a retrievable filter in Europe, it has not received FDA approval for this application. Several Canadian medical centers have reported successful retrieval of this filter using an endovascular approach within 12 to 14 days after insertion. Recent reports state that the filter can actually be repositioned every seven days; this potentially increases the likelihood that it can be removed.[93]

Millward et al.[94] reported the results of placement of Gunther Tulip filters from eight hospitals in 90 patients. Filter retrieval was attempted in 52 patients with 53 filters, and was successful with 52 filters. The duration of filter implantation was two to 25 days with a mean implantation time of nine days. Fifty-one patients were monitored for a mean of 103 days after filter retrieval. Four patients (8%) required reinsertion of a permanent filter from 17 to 167 days after filter removal, because of either bleeding from anticoagulation or requirement for further surgery. Of patients in whom filters were successfully retrieved, one patient had recurrent DVT at 230 days after filter retrieval. In 39 patients in whom the filter was not retrieved (a mean follow-up of 85 days), two filter occlusions (5%) were noted. No other complications of filter placement were noted.

TrapEase Filter

The TrapEase caval filter (Cordis; see Figure 46.4), approved by the FDA in 2002, is a symmetric double-basket caval filter constructed from nickel-titanium (nitinol) material. It is a small profile filter that is inserted through a 6 Fr introducer. It has a unique biconvex symmetric filter that allows a single filter to be placed from either direction. This filter has six struts that frame the filter in a diamond or trapezoidal configuration and ends in two superior and inferior baskets created by six struts converging at the apex of the filter. Proximal and distal hooks are fixed at the straight struts that parallel the wall of the cava. The superior basket is conical and oriented in the conventional concave position. The inferior basket is oriented in a mirror position with the apex pointing inferiorly (see Figure 46.4). The hook is

placed at one apex of the filter for manipulation and possible retrieval of the filter. The filter can be inserted through the femoral, jugular, subclavian, or antecubital vein.[55,57] The deployed filter measures 50 to 62 mm in length and approved for vena cavas <30 mm in diameter. This filter is MR-imaging compatible.

Rousseau et al.[95] reported the results of a small French multicenter prospective trial to evaluate the TrapEase IVC filter. A total of 65 patients who had DVT with recurrent PE, free-floating thrombus, or both, with contraindications to anticoagulation (37 patients), or with complications in achieving adequate anticoagulation (28 patients) were enrolled in 12 centers throughout Europe and Canada. These patients were evaluated at 10 days, one, three and six months with clinical evaluation, abdominal x-ray, duplex ultrasound, and abdominal CT scanning. They reported a 95.4% technical success rate in filter placement with a clinical success rate of 100% at six months (with no symptomatic PE). There was no filter migration, filter fracture, vessel wall penetration, or insertion site thrombosis during this short follow-up period. Two patients had early IVC thrombosis within 30 days, one was symptomatic (1.5%) and was treated with thrombolysis; and the other one was asymptomatic.

Schutzer et al.[96] reported the results of a retrospective study of 189 consecutively inserted infrarenal TrapEase filters at a single institution over a 22-month period. The technical success was 100%. They noted 1.5% of symptomatic caval thrombosis. The authors reported one case of symptomatic PE after TrapEase filter placement. There was also one case report of intracardiac migration of a TrapEase filter.[97]

COMPARISON OF VARIOUS PERMANENT IVC FILTER DEVICES

Table 46.2 summarizes various commonly used caval filters. As noted from this table, a majority are comparable in regard to their effectiveness in preventing recurrent PE, with some variation in regards to the incidence of IVC thrombosis and DVT. They also vary somewhat on the rates of migration.

FOLLOW-UP AFTER IVC FILTERS

There is no specific protocol for late follow-up of patients receiving IVC filters, especially when the patient is asymptomatic. It is generally believed that a simple physical examination in conjunction with a plain abdominal x-ray can detect the majority of complications of IVC filters. CT scanning and duplex ultrasonography are helpful to assess any abnormalities. Venography should be reserved for patients in whom these modalities are not helpful.

CONCLUSIONS

Many different and ingenious caval filters are currently available on the market for clinical use. The perfect filter has yet to be developed. It appears likely that caval filters do reduce the incidence of PE, but may result in IVC thrombosis and a higher incidence of recurrent lower extremity DVT than what is seen with anticoagulation alone. Prospec-

TABLE 46.2 Comparison of Various IVC Filters

Filter (ref)	Carrier	Type of evaluation	No.	F.U. (mos.)	Recurrent PE	IVC thrombosis	DVT	Migration rate (%)	Misplacement rate (%)
Stainless steel Greenfield (61)	24 F	Meta-analysis	3184	18 (1–60)	2.6% (0–9%)	3.6% (0–18%)	5.9% (0–18%)	35%: >3 mm	4%
Titanium Greenfield (61)	12 F	Meta-analysis	511	5.8 (0–81)	3.1% (0–3.8%)	6.5% (1–31%)	22.7% (0–36%)	11%: >9 mm	0.5%
Stainless steel over-the-wire Greenfield (98)	12 F	Case series	599	26	2.6%	1.7%	7.3%	—	—
Bird's Nest (61)	12 F	Meta-analysis	1426	14.2 (0–60)	2.9% (0–4.2%)	3.9% (0–15%)	6% (0–20%)	9%	—
Simon nitinol (61)	7 F	Meta-analysis	319	16.9 (0–62)	3.8% (0–5.3%)	7.7% (4–18%)	8.9% (8–11%)	1.2%	—
VenaTech (61)	12 F	Meta-analysis	1050	12 (0–81)	3.4% (0–8%)	11.2% (0–28%)	32% (0–32%)	14%: <10 mm	—
VenaTech Low Profile	6 F	—	30	2.3	0%	0%	10.3%	—	—
Gunther Tulip (99)	8.5 F		83	4.5 (0–36)	3.6%	9.6%	—	—	—
TrapEase (97)	6 F	Clinical trial	189	(0–24)	0%	1.5%	—	—	—

—, none or not reported.

tive randomized trials comparing the efficacy of filters and comparing various filter devices are presently lacking. Each of these filters has its own advantages and disadvantages, therefore the physician must select a filter that is suitable to the patient and the one with which he or she is familiar. Because of concerns over the long-term performance characteristic of caval filters, it is best to adhere to strict indications for filter insertion.

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CHAPTER

47

Complications of Vena Cava Filters

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BACKGROUND

Venous thromboembolism (VTE) is optimally treated by anticoagulation. When anticoagulation must be withheld, inferior vena cava interruption affords protection against major embolic events likely to be life threatening. Inferior vena cava (IVC) interruption historically has progressed from cava ligation to plication, caval clips, surgically inserted caval umbrellas and filters, and finally to percutaneously inserted filters. Complications associated with the historic methods of caval interruption and devices have driven, and will continue to encourage, the modification and design of devices that have limited endothelial cell interactions, require smaller deployment tools, and use imaging friendly materials with reduced thrombogenicity.

Currently available devices include permanent filters that once deployed remain in place indefinitely and optionally retrievable filters that may be left in place permanently or may be removed within a specified time frame (weeks to months depending on the device). Retrievable filters are similar in appearance and design to permanent filters, but have modifications to the caval attachment sites and/or hooks at one end to facilitate their removal. They have been designed to take advantage of the effectiveness of a permanent filter and yet minimize the complications of a long-term indwelling vascular device. The underlying premise for retrievable filters is based on the concept that absolute contraindications to systemic anticoagulation may be short-lived and the long-term outcomes of IVC filters may not necessarily be as benign as previously considered. This is particularly true for young patients who may require an IVC filter, thus exposing them to a lifetime of risk of developing a filter-related complication and the risk associated with anticoagulation (if feasible) to prevent filter thrombosis. The decision regarding the use of a permanent or optionally retrievable filter must be made individually for each patient.

Current accepted indications for IVC filter use include contraindications to anticoagulation (active bleeding or recent hemorrhage), complications of anticoagulation, or thromboembolism (pulmonary embolism or recurrent/propagation of deep venous thrombosis [DVT]) despite adequate anticoagulation.[1] These accepted indications are frequently expanded to include relative indications including individuals with extensive pulmonary embolism (PE) or venous thrombosis such as free-floating thrombus, patients undergoing venous thrombolysis, patients with significant underlying cardiopulmonary disease in whom pulmonary embolism may pose a significant threat to survival, and patients undergoing pulmonary thromboendarterectomy. In some centers IVC filters are used for primary prophylaxis against pulmonary embolism for patients who have sustained major trauma and cannot receive recommended pharmacologic or mechanical regimens for prophylaxis, or as adjuvant prophylaxis in patients undergoing high-risk procedures with an increased risk for venous thromboembolism.[2] With these indications in mind it is important to recognize that an IVC filter does not treat venous thromboembolism but rather protects that patient from the most serious adverse event, massive, fatal pulmonary embolism. Most physicians would agree that anticoagulation should be commenced despite the presence of a filter when deemed safe. However, there are no recommendations regarding the duration of anticoagulation in this setting.

Filter placement for VTE treatment as well as prophylaxis has increased. In a recent population based study of IVC filter use in California, 9665 IVC filters were placed over a four-year period, from 1991 to 1995. During this period there was a 40% increase in the number of ICV filters

placed, from 1446 in 1991 to 2447 in 1995. Overall, 6.6% (4044/61,188) of patients admitted with a principal diagnosis of VTE received an IVC filter. Sixty percent (5621/9665) of the filters in this study were deployed in patients lacking a primary diagnosis of VTE (i.e., used for primary or secondary VTE prophylaxis).[3] Stein et al. analyzed the National Hospital Discharge Survey (NHDS) database for information on IVC filter use over a 21-year period. The number of IVC filters inserted increased from 2000 in 1979 to 49,000 in 1999. In 1999, 45% of filters were placed in patients with DVT, 36% in patients with PE, and 19% of IVC filters were placed in patients without a coded diagnosis for VTE.[4] Registries of patients treated for VTE have demonstrated IVC filter insertion rates of 2% in Spain compared to 14% in a U.S. study.[5,6] In the U.S. study, 33% of IVC filters were inserted for primary treatment for DVT and 17% were placed for indications other than the three currently accepted indications for IVC filter use.[6] The robust use of IVC filters for prophylaxis and for relative indications is interesting in view of the lack of comparative data or prospective, randomized trials regarding IVC filter use. Indeed most of the literature on the use and complications of IVC filters is derived from case series, retrospective studies, or prospective trials enrolling fewer than 100 patients.[7]

Several comprehensive reviews of IVC filters and filter complications have been published detailing the design, deployment, and complications of both the permanent and optionally retrievable filters.[8–11] The use and complications of the stainless steel Greenfield filter and its modified designs have been studied more thoroughly than other filters. Considerably less literature is published regarding the most recently approved permanent filter, the TrapEase, or the optionally retrievable filters, the Günther-Tulip, OptEase, and Recovery filters. One can only assume that these filters will have the same success and complication rates as the devices that have a longer history of use. Certainly IVC filters appear to prevent major pulmonary embolism in patients with DVT; however, complications related to IVC filter use are not negligible. Complications may include venous thrombotic events, deployment and positioning issues, insertion site complications, and migration after placement. Table 47.1 lists complications documented with permanent or optionally retrievable IVC filters. There are no large case series or comparable studies examining the true rates of complications by filter type. It is also important to note that there is usually no radiologic follow-up after filter placement and many complications, such as minor degrees of filter migration, limited penetration through the caval wall, or even minor compromise of the structural integrity of the filter, may be clinically silent. Currently, there are no guidelines for identifying patients who should undergo radiographic follow-up post vena caval filter placement. Major complications related to IVC filters, such as migration or significant caval perforation, are relatively rare. Life-threatening complications are uncommon. Four (0.16%) filter-related deaths were noted in one review.[12] The most common complications are thrombosis including recurrent DVT, PE, IVC, or filter thrombosis and insertion site thrombosis. For this reason, when a short-term contraindication to anticoagulation has resolved, some practitioners advocate long-term anticoagulation in patients with vena caval filters.

TABLE 47.1 Complications Related to Inferior Vena Cava Filters

Venous thromboembolism
Recurrent deep venous thrombosis
Thrombus propagation
Recurrent pulmonary embolism
Insertion site thrombosis
Insertion site complications
Insertion site thrombosis
Hematoma/hemorrhage
Infection
Deployment complications
Tilting
Malposition in the incorrect vein/vessel
Failure to fully deploy
Device complications
Strut fracture
Guidewire entrapment
Migration (proximally or distally)
Extrusion through the vena cava to adjacent structures
Retrieval complications
Failure to retrieve
Device fracture
Retained struts/hooks

Although retrospective studies examining the use of anticoagulation following IVC filter placement have not demonstrated decreased incidence of recurrent DVT,[13] recurrent venous thromboembolism is clearly the most common complication of IVC filters. Because of this, anticoagulation should be initiated when possible even after an IVC filter has been placed. Guidelines have been published regarding current anticoagulation recommendations. It is unclear at this time whether the presence of an IVC filter should extend the duration of anticoagulation for a particular clinical situation.[14] For now, the duration of anticoagulation must be individualized for each patient.[1]

THROMBOTIC COMPLICATIONS

Unfortunately, thrombotic complications after IVC filter placement have not been studied thoroughly. The only prospective, randomized trial of IVC filter outcomes was performed by the PREPIC study group. Four hundred patients with proximal DVT at risk for PE were randomized to receive an IVC filter followed by anticoagulation or to

TABLE 47.2 Two-Year and Eight-Year Results of the PREPIC Trial of IVC Filter Use to Prevent Pulmonary Embolism[15,16]

	Recurrent DVT[a]		Symptomatic PE[b]	
	2 Years	8 Years	2 Years	8 Years
Filter	20.8%	35.7%	3.4%	6.2%
No Filter	11.6%	27.5%	6.3%	15.1%
P	0.02	0.16	0.042	0.008

[a]DVT = deep venous thrombosis; [b]PE = pulmonary embolism.

anticoagulation alone (either unfractionated heparin or low-molecular weight heparin followed by vitamin K antagonists). Two reports addressing recurrent DVT, pulmonary embolism, IVC thrombosis, and post-thrombotic changes were published.[15,16] There was no significant difference in the duration of anticoagulation between the two groups.[16] At both two and eight years of follow-up there was a significantly increased risk of recurrent DVT in patients with an IVC filter compared to patients without filters (see Table 47.2). At two years there was no difference in the rate of symptomatic pulmonary embolism between the groups; however, by eight years of follow-up there was a 63% decrease in the risk of recurrent PE in patients receiving an IVC filter compared to patients without (see Table 47.2).[15,16]

Deep Venous Thrombosis

Recurrent deep venous thrombosis after IVC filter placement may include propagation of an existing thrombus into additional venous segments, involvement of a new venous segment including the contralateral limb, or insertion site thrombosis. A comprehensive review of IVC filters by Streiff in 2000 compiled the reported complications from available filters including the stainless steel Greenfield (SSG), titanium Greenfield (TG), Bird's Nest (BN), Simon Nitinol (SN), and VenaTech (VT).[9] Most included studies were either retrospective reviews or prospective follow-up performed by chart review, questionnaires, or clinic visits as opposed to serial radiographic surveillance. In Streiff's review the SSG and the BN filters had the lowest rates of recurrent deep venous thrombosis, 5.9% and 6%, respectively.[9] The highest rates of DVT have been seen with the TG (22.7%), the VT (32%), and the TrapEase (45.7%).[9,10] However, these results were generated from small studies with very few enrolled patients.

Since there are no prospective comparative studies of IVC filters, it is difficult to determine whether the risk of recurrent venous thrombosis relates to the presence of a filter or if specific design issues are related to thrombogenesis. The PREPIC trial, which used the VenaTech and the Titanium Greenfield filters in 56% and 26.5% of patients, respectively, documented increased risk of recurrent symptomatic DVT in patients with filters compared to patients without a filter.[15] Although is unlikely that comparative studies of specific devices will be performed, further study of filter design and thrombosis may help clarify factors contributing to thrombosis.

Deep venous thrombosis at the insertion site has been documented following IVC filter placement. With routine surveillance, insertion site thrombosis has been identified in 14 to 64% of patients. Since IVC filters may be inserted by femoral, jugular, or brachial routes, insertion site thrombosis may occur in an unprotected venous bed.[9] The newer low-profile delivery systems being developed may decrease the risk for insertion site thrombosis. To document the actual frequency of this complication, however, studies will need to incorporate routine surveillance of the insertion site into protocols.

Post-Thrombotic Syndrome

After a DVT, clinical symptoms of the post-thrombotic syndrome increase over time. At eight years follow-up, post-thrombotic symptoms are observed in approximately 70% of patients with or without IVC filter placement.[15] Given the high rate of post-thrombotic complications in patients with VTE, recurrent symptoms of discomfort, erythema, edema, and increased warmth are not uncommon. If recurrent deep venous thrombosis is suspected, patients should undergo further evaluation. Imaging with venous duplex ultrasound or venogram may be used to determine whether the patient has had proximal or distal propagation of existing thrombus or recurrent DVT in a new venous segment. In some cases determining the age or chronicity of the thrombus is difficult. In this setting D-dimer measurement may assist in making this determination. Compression stockings are recommended following a DVT with or without IVC filter placement to decrease the risk of post-thrombotic syndrome symptoms.

Pulmonary Embolism

IVC filter placement is one method of managing DVT and preventing PE in patients unable to be anticoagulated. However, despite IVC interruption, pulmonary embolism may occur. The origin of pulmonary emboli in this setting includes propagation of thrombus proximal to the IVC filter (see Figure 47.1), small emboli that pass through the filter, emboli from unprotected venous beds including the upper extremity, or embolism through developed pelvic or abdominal veins or collaterals such as the azygous or ovarian vein. Cumulative rates of recurrent symptomatic PE in the PREPIC trial were 1.1%, 3.4%, and 6.2% at 12 days, two years, and eight years follow-up, respectively. Two patients (1%) suffered fatal PE.[15,16] From the reviews by Streiff and Kinney, 40 studies of the SSG filter demonstrated a

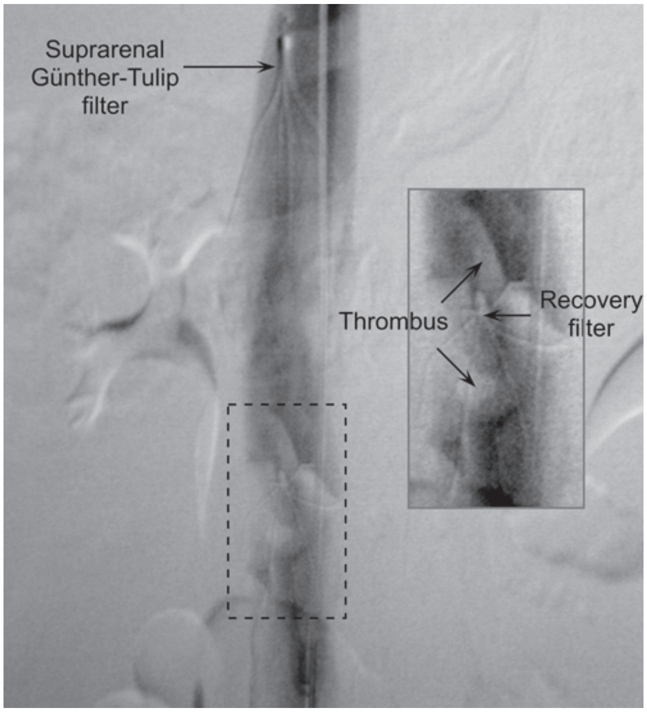

FIGURE 47.1 Thrombus both within and above a filter (inset) demonstrated by venogram in a patient who developed massive pulmonary embolism despite the presence of an infrarenal Recovery filter. A suprarenal Günther-Tulip filter was placed to protect against further embolism until anticoagulation could be initiated.

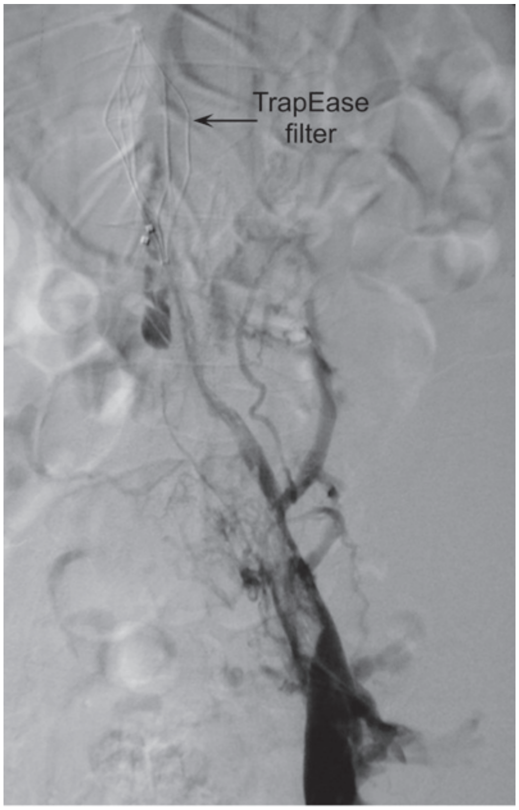

FIGURE 47.2 Chronic IVC and filter thrombosis demonstrated below a TrapEase filter. Collateral venous drainage is noted.

composite rate of pulmonary embolism of 2.6%, with a range between 0 to 9%.[9,10] The composite rates for the other available filters were TG 3.1% (range 0–3.8%), BN 2.9% (range 0–4.2%), SN 3.8% (range 0–5.3%), and VT 3.4% (range 0–8%). The rates of fatal pulmonary embolism were between 0.3% in the VT series up to 1.9% for the SN filter.[9,10] Athanasoulis et al. documented a fatal PE rate of 3.7% following filter insertion in a 26-year review of their IVC filter experience.[17] No recurrent PE was documented in the single trial using the TrapEase filter.[18] The rates reported for recurrent symptomatic pulmonary embolism and fatal pulmonary embolism are not negligible. Studies have not addressed clinical conditions likely to predispose to this complication.

In a patient with suspected pulmonary embolism, PE protocol chest computed tomography (CT), pulmonary angiography, or ventilation/perfusion nuclear medicine lung scanning should be performed. If the diagnosis is confirmed, the source of the event should also be identified. IVC filter thrombosis can be investigated using contrast enhanced abdominal CT with venous phase imaging or contrast vena cavography. Duplex ultrasound of unprotected venous beds should also be performed to evaluate other potential sources of embolism.

Inferior Vena Cava Thrombosis or Occlusion

IVC thrombosis may result from innate thrombogenicity of the filter, trapped emboli within the filter, or propagation of thrombus through the venous system up to and including the filter (see Figure 47.2). The PREPIC trial documented symptomatic IVC thrombosis in 13% of patients after eight years of follow-up.[16] Other reports have documented IVC filter thrombosis rates from 0 to 31%. Once again the SSG and BN filters have documented the lowest rates of IVC thrombosis, 3.6% and 3.9%, respectively. The highest rates of IVC thrombosis occurred with the VT filter, 11.2%.[9] In initial studies, the TrapEase filter had a documented IVC filter thrombosis rate at six months of 3.1%.[18]

Studies of optionally retrievable filters have documented IVC thrombosis in 0 to 9.6% of patients with the Günther-Tulip filters.[11,19] In addition, thrombus trapped within the filter at attempted retrieval has been documented in 10% of Günther-Tulip and 22% of Recovery filters, suggesting the filters may have performed well in preventing pulmonary emboli,[11] but this could lead to eventual caval thrombosis if the filter is not removed. Longer follow-up is required to determine if the rates of IVC thrombosis in optionally

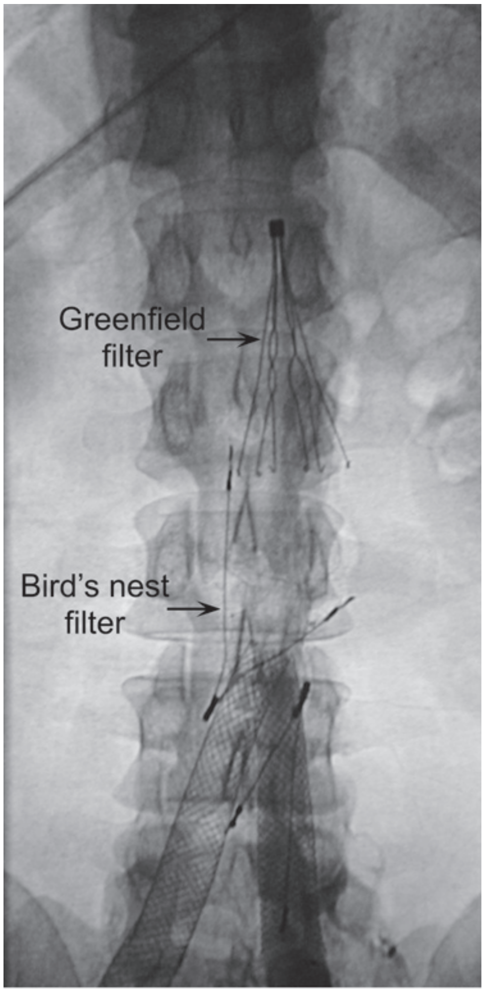

FIGURE 47.3 Bilateral iliac vein stents in a patient with chronic venous occlusion following Bird's Nest and Greenfield filter placement.

retrievable filters will remain constant or increase over time.

When IVC thrombosis is identified, or if the source of the pulmonary embolism is suspected or documented to be due to thrombosis proximal to the filter, management must be individualized. One option is placement of a more proximal vena caval filter, typically suprarenal placement (see Figures 47.1 and 47.3). The major concern in this setting is the continued propagation of the thrombus with the potential for involvement of the renal veins. In the hands of a skilled interventionalist, filter thrombosis can be managed by endovascular techniques (see Figure 47.3). Mechanical and pharmacologic thrombolysis may be used to restore patency of the IVC filter.[20–22] Other endovascular techniques including balloon maceration of the thrombus or stent placement to collapse the filter and exclude it from the IVC have been reported.[20,23]

INSERTION SITE COMPLICATIONS

Insertion site complications after filter placement have perhaps the most varied manifestations. These complications occur in 4 to 11% of all filter insertions.[10] Some are site dependent, and others may be directly related to the device delivery system. Insertion site complications range from minor bleeding to major complications that may be the source of significant morbidity and, in fact, mortality. Death related to IVC filter insertion has been reported to occur in 0.12%.[10]

Most of the complications are similar to other procedures in which central venous access is obtained; bleeding (major or minor), arteriovenous fistula, infections, vessel damage/rupture, and access site thrombosis. Some of the vascular complications at the access site are considered to be directly related to the profile of the delivery system. This has been a major reason for the development of the newer filter types, such as the TrapEase, with a lower profile delivery system, which limits the size of the venipuncture and potentially decreases these complications. The internal jugular vein is often a preferred site of access but, due to its anatomic proximity to vital structures, complications related to access at this site may have devastating consequences. Stroke caused by inadvertent carotid puncture, pneumothorax, vocal cord paralysis caused by damage to the recurrent laryngeal nerve, arrhythmia, and air embolism all have been documented.

DEPLOYMENT COMPLICATIONS

Complications that may occur at the time of filter placement are largely dependent upon the equipment used to deploy the filter as well as the filter type. These complications may be generalized into tilting or malposition, incorrect anatomical placement, or failure of the device to fully deploy at its intended site. The incorrect deployment of a filter has many clinical implications and possible secondary complications. An incorrectly deployed filter may not achieve the desired effect of protection from pulmonary embolism and yet exposes the patient to all the complications of the procedure, the potential for migration, as well as subsequent complications of thrombosis as previously discussed. In addition, the patient and the physician may derive a false sense of security knowing a filter has been placed despite the suboptimal deployment.

Malpositioning

Filter malpositioning or tilting is a complication of vena caval filter insertion that theoretically may result in inadequate protection from pulmonary embolism. For permanent filters, this traditionally is managed with either observation

or additional filter placement, typically in the suprarenal position. In a single-center study of 486 patients undergoing duplex ultrasound-guided (n = 435) or intravascular ultrasound (IVUS)-guided (n = 51) IVC filter insertion by Corriere et al., 12 patients (2.4%) had inadequate positioning as determined by postoperative radiography.[24] Two of these patients had no further filter manipulation, three had a second filter placed under fluoroscopic guidance, and five patients had filters retrieved and repositioned under fluoroscopic guidance. All five patients undergoing retrieval and repositioning in this series had Greenfield filters, which are not traditionally regarded as retrievable. This manipulation was possible with advanced endovascular techniques.[24] In another long-term study of Greenfield filters followed by abdominal radiography, Messmer et al. reported five patients (7%) in whom the filter was at an angle of more than 16 degrees from the vertical.[25] A change in filter angle may result from displacement of a strut into the right renal vein as well as from physiologic changes.[25] Retrievable filters typically are manipulated at the time of insertion to achieve minimal tilting. In the review by Stein et al., 12% of Günther-Tulip filters were tilted. In one small study of Recovery filters, 6% demonstrated tilting.[11]

The effect of IVC filter tilt and asymmetry on filter function is considered controversial. The clinical concerns include reduced protection from emboli due to a larger space between the struts allowing transit of thrombi as well as a potential for increased thrombogenicity due to flow disturbances from the asymmetric filter struts along the vessel wall. A study conducted by Katsamouris et al. demonstrated when centered, the original Greenfield IVC filter allowed passage of small clots, and eccentric positioning (defined as >14º) allowed small and large clots to pass through.[26] Another study by Greenfield and Proctor showed that alignment only assumed importance when the IVC is larger than 22 mm.[27] A clinical study evaluated recurrent PE and caval thrombosis in patients with titanium Greenfield IVC filters and a subgroup that had filter asymmetry, defined by strut pattern in the cava. Out of a total of 738 filters, asymmetry was found in 42 cases (5%). A total of three of 35 patients (8.6%) with asymmetric filters had recurrent PE compared to 11 episodes of recurrent PE (3.3%) among 338 patients with symmetric IVC filters.[28] The difference was not statistically significant.

Although it is difficult to know exactly how tilting or malpositioning affects the functioning of a given device in view of the lack of routine clinical follow-up; device modifications have been used to reduce this complication. The currently available Greenfield filters use a guidewire deployment system designed to promote mid-line deployment. The TrapEase and OptEase devices have adopted a symmetric filter design to optimize vertical deployment. Modifications such as a dual level filter design have also been used to provide more efficient thrombus trapping.

Inadvertent Deployment in an Incorrect Vessel

There are reports in the literature documenting filter deployment in the incorrect vessel or location. In some cases this may be due to anomalous venous anatomy, emphasizing the importance of vena caval imaging prior to filter deployment. Imaging has historically been performed by venography/cavography using iodinated contrast, gadolinium, or occasionally carbon dioxide. More recent reports have focused on using duplex ultrasound or IVUS, which may allow for bedside insertion in patients who are critically ill or if transportation is difficult due to extensive spine or orthopedic injuries. Vena cava anomalies such as megacava (>30 mm), small caliber cava, congenital absence of the vena cava, double cava, left-sided vena cava, or thrombus within the cava may be documented. Renal vein abnormalities such as circumaortic veins, retroaortic veins, multiple renal veins, or congenital absence of the kidneys may also be documented. In one study, anatomical variation or IVC thrombosis was documented in 9.6% of patients prior to deployment that warranted an adjustment in the deployment strategy in 4% of patients.[17]

The usual site of filter deployment is the infrarenal IVC. There are clinical situations that may warrant the placement of the filter in locations other than the infrarenal inferior vena cava. Suprarenal IVC and superior vena cava (SVC) deployments are discussed elsewhere in the chapter. There are other untraditional locations of filter placement such as the iliac vein in patients with a mega cava >40 mm. This of course does not constitute an inadvertent misplacement. However, misplaced filter deployment has been documented in the right atrium,[17] the innominate vein,[29] above the renal veins, juxtaposed to the renal veins, or partially within a renal vein,[17] and in the iliac vein.[30] Although a misplaced filter is an unusual complication and in most cases is tolerated without clinical effect, serious consequences may occur in some settings and the utmost care should be used to avoid inadvertent deployments.

Failure to Deploy

The failure of vena caval filters to deploy fully is discussed frequently, but rarely documented in the literature (see Figure 47.4). Although this complication may manifest as filter migration or even embolization, most cases are well tolerated without clinical consequence. Partial deployment usually has been attributed to a malfunction of the filter itself that occurs on a case-by-case basis and is not necessarily design specific. In one study of VenaTech filters, major complications of placement occurred in three patients, all when the right internal jugular vein was used for introduction. One filter was inadvertently placed in the right renal vein and two of the filters failed to open fully.[31] Deployment

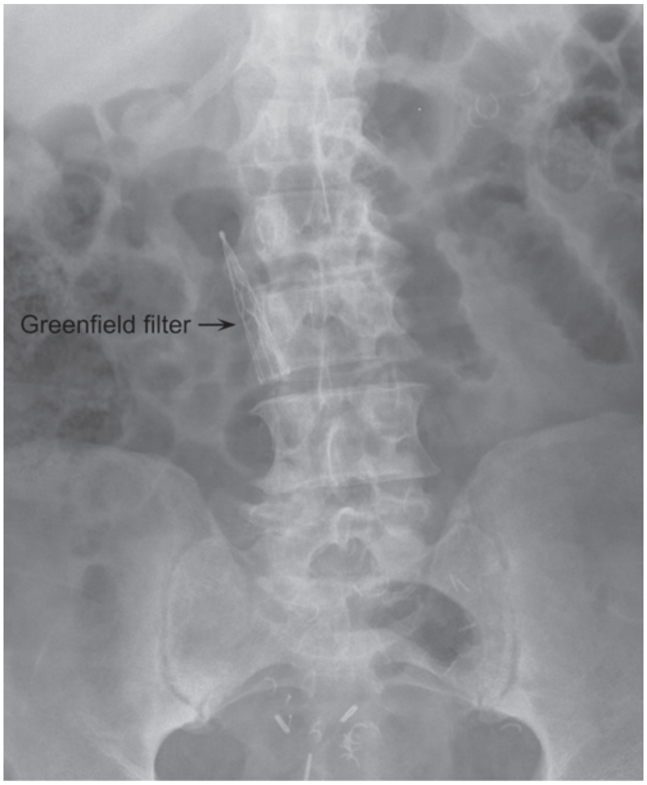

FIGURE 47.4 Partial deployment of this Greenfield filter was documented by abdominal radiograph.

complications with the Greenfield filter and modified designs have been documented in another series.[17] The TrapEase filter has not demonstrated failure to deploy; however, filter shortening and maldeployment has been documented.[18] In many cases the failure to open fully can be addressed at the time of filter placement. There are rare reports of endovascular manipulation of under or partially deployed filters.

DEVICE COMPLICATIONS

Impetuses for the development of different delivery systems and different filter designs are complications that are device and equipment specific. Strut fracture due to compromise of the structural integrity of the filter is one concern. It is a rare complication; however, strut fracture has been documented for most filter designs.[17] To date there are no large comparative case series among filter types specifically addressing this issue. Usually the identification of a strut fracture is a serendipitous discovery during radiological imaging performed for entirely different clinical indications. Clinical issues may arise when a fractured strut is extruded through the IVC into adjacent structures. The most vulnerable points for fracture are welded seams. To this extent filters such as the TrapEase, which are laser cut in a unibody style, are less likely to have fracture complications. Although retained filter struts or hooks (depending upon filter design) are theoretical complications of optionally retrievable filters, there are no reports of clinical series that address these complications.

Guidewire entrapment is another device-related complication that may occur at the time of filter placement or when a wire is passed through the filter for central access. In one *in vitro* study, the TrapEase filter entrapped 3.0-mm and 1.5-mm J-tipped guidewires, whereas the VenaTech LP (low profile) and Günther Tulip filters did not.[32] Another study described entrapment of both the 1.5-J and 3-J guidewires by the stainless steel Greenfield and VenaTech LGM devices.[33] The 1.5-J guidewire became entrapped regardless of engagement pattern, whereas the 3-J became entrapped only when engaged in the hole in the apex of the SSG and VT filters. In a series of SVC filters, 56% of patients had subsequent central access without complications.[34] In another series one filter was dislodged during central line placement and repositioned into the innominate vein.[29] Displacement into an iliac vein should be an uncommon complication. This complication may be avoidable if fluoroscopy is used during central access in patients with residing filters. Retrieval of an entrapped guidewire can be a technically challenging proposition. There have been isolated reports in the literature of using a snare and other such endovascular devices for percutaneous retrieval.

MIGRATION

Filters are long-term intravascular devices that are subject to a number of external forces that may change their position as well as dimensions over time.[35] These changes can result clinically in filter migration or penetration/extrusion through the vessel wall. Case series have documented migration in all filter types.[8] The VenaTech filter appears to be most affected by this complication; up to 18% migrated in one study.[8] Migration may be either cephalad and caudal; typically movement >20 mm is considered clinically significant. In a long-term study of 69 patients with a Greenfield IVC filter in place for one to nine years evaluated with supine abdominal radiographs, the filter span diameter had increased by 3 to 11 mm in 22 (32%) patients, and had decreased by 3 to 18 mm in six patients (9%). Twenty patients (29%) had caudal migration of 3 to 18 mm, and four (6%) had cephalad migration.[25]

In some cases migration to clinically significant structures such as the intrahepatic IVC (see Figure 47.5) or the right atrium may occur.[17] A number of case reports describe serious complications of cephalad embolization to the heart, including pericardial tamponade and intracardiac migration with life-threatening arrhythmias.[36,37] Retrieval of these filters has been attempted using endovascular techniques.

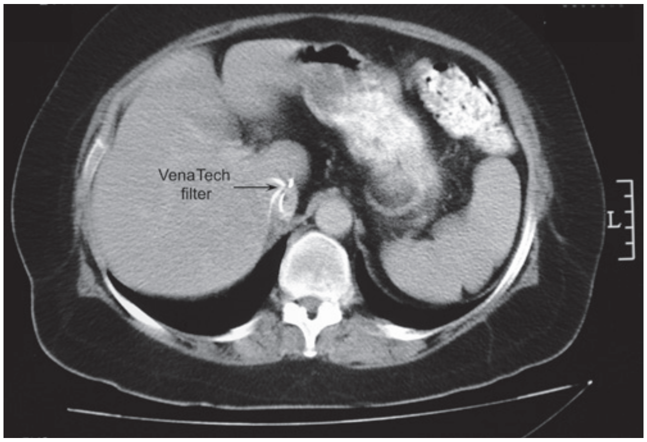

FIGURE 47.5 VenaTech filter with migration to the level of the intrahepatic inferior vena cava demonstrated on CT scan.

However, because of the unusual location, retrieval may require extraordinary measures such as placement on cardiopulmonary bypass, circulatory arrest, and even open surgical procedures. Occasionally, embolization is considered to have occurred because of a large thrombus burden entrapped within the filter.[19,35] Routine clinical follow-up and serial radiographic surveillance has not been advocated following IVC filter placement, so migration usually is identified serendipitously unless a serious clinical consequence occurs.

EXTRUSION

Most filters will have some change in dimension following placement.[35] Extrusion of the filter struts through the caval wall is a near-universal phenomenon.[8,35,38] In a study to determine the long-term clinical and radiographic outcome of patients who undergo insertion of a Bird's Nest filter, perforation of the caval wall was universal but not clinically symptomatic.[39] Strut extrusion usually does not assume clinical importance until there is involvement of adjacent structures and associated clinical complications.

There are a number of case reports in the literature detailing individual clinical experiences and unusual complications resulting from strut or even filter extrusion from the IVC. Reports of small bowel obstruction occurring as a result of volvulus occurring around an extruded filter strut,[40] a fragmented IVC filter penetrating the aorta and causing a small infrarenal aortic pseudoaneurysm,[41] hydronephrosis caused by transcaval penetration of a Bird's Nest filter,[42] laceration of a lumbar artery by a stainless steel Greenfield filter strut that resulted in a near fatal hemorrhage[43] and upper gastrointestinal bleeding secondary to Bird's Nest inferior vena caval filter migration into the duodenum[44] appear in the literature. These are rare, usually reportable, complications of filter placement.

RETRIEVAL COMPLICATIONS

The optionally retrievable filters, the Günther-Tulip, OptEase, and Recovery filters, differ in shape, contact with the IVC wall, and recommended dwell time. Each of these filters is approved by the FDA for retrievable use. When used as an optionally retrievable filter, two visits to the interventional suite are required; initially for placement and when indicated for removal. This creates a potential for increased numbers of complications related to venous access as well as an entirely new category of complications related to the explantation of devices. Furthermore, explantation complications can be of a serious nature (e.g., caval perforation).

The maximal dwell time for retrievable filters when safe retrieval is possible has not yet been evaluated. Binkert et al.[45] have reported the retrieval of such a type of filter at 317 days without complication on follow-up venogram. Compared to the Recovery filter, the recommended time to removal is relatively short for the Günther-Tulip and OptEase filters. Repeated repositioning has been used to prolong the deployment of these devices.[46] Most of the optionally retrievable filters are relatively new, and little to no data are available on their long-term performance when used as permanent filters. Although most retrievable IVC filters are placed in patients with a well-defined, short-term risk for VTE and contraindications to anticoagulation, the percentage of retrievable filters actually removed is less than 50%.[47] The most common reason stated for not retrieving a filter is due to caval or filter thrombus or continued contraindication to anticoagulation. All retrieved filters have strands of organized thrombus on the filter struts. The presence of small thrombi does not dictate the need to abort the retrieval, but larger thrombi preclude filter removal. Given the large numbers of these filters remaining *in situ*, data on the potential longer term complications of these filters should be emerging.

Data on failed retrievals based on technical difficulties are sparse. Most limited case series of the various filter types report successful snaring and device retrieval with no caval injuries.[48,49] In one series, retrieval failure was related to device angulation within the vena cava that precluded safe capture.[48] Difficulties with retrieval may be encountered more frequently with longer dwell times, but data are lacking at present.

SPECIAL CONSIDERATIONS

There are identified patient populations in whom IVC filter use generates special consideration. These include

trauma patients, children, pregnant women, and patients with septicemia. In the trauma population IVC filter placement has gained popularity as a mechanism of both primary and secondary prophylaxis. The body of literature regarding filter use in this setting is growing. On the other hand, very few studies focus on filter placement in children, during pregnancy, or in patients with septicemia.

In most clinical settings filters are deployed into the infrarenal IVC. However, placement in the suprarenal IVC or SVC has also been used. Suprarenal placement may be indicated in some clinical settings or may occur inadvertently during deployment. SVC positioning has been employed to protect against embolism from upper extremity DVT.

Trauma

The use of IVC filters for primary prophylaxis in trauma patients has increased, especially when sequential compression or pharmacologic therapy is contraindicated; for example, vertebral fracture or spinal cord injury, multiple lower extremity fractures, and closed head injury. The use of IVC filters for primary prophylaxis in this setting is open to controversy. Analysis of 450,375 patients registered in the American College of Surgeons National Trauma Data Bank identified a VTE (DVT, PE, or both) rate of 0.36%. Mortality rate in patients with PE was 18.7%. A total of 3883 patients had IVC filters placed; 83% were prophylactic. This analysis also identified risk factors for VTE including age ≥40 (OR 2.29), pelvic or lower extremity fracture (OR 2.93 and 3.16, respectively), spinal cord injury with paralysis (OR 3.39), head injury (OR 2.59), > three days of ventilator dependency (OR 10.62), venous injury (OR 7.93), shock (OR 1.95), and major surgery (OR 4.32).[50] Yet data regarding IVC filter use in the trauma setting are based solely on case series reports and retrospective registry studies. Girard et al. reviewed 16 case series published before 1999 with a total of 1112 trauma patients.[51] Pulmonary embolism occurred following IVC filter placement in 0 to 3.9% of cases. Fatal pulmonary embolism was documented in a single patient in each of two studies. DVT was identified in 0 to 20.6% of patients. IVC thrombosis or occlusion occurred in 0 to 6.7% of cases. Insertion site thrombosis and procedural complications were identified in 0 to 5.7% and 0 to 4.6% of cases, respectively.[51] The results do not support the general use of filters in all trauma patients, but since this review encompassed reports prior to 1999, the use of newer, low profile devices may demonstrate more favorable results. Furthermore, selected use of filters in high-risk subgroups of trauma patients may be appropriate.

Optionally retrievable filters have also been used in the trauma population. In recently published series, recurrent DVT was documented in 2.9% and 8.6%; and in one study, insertion-site DVT was documented in 1.9%.[30,52] Filter retrieval was successful in 51% and 66% of patients. If the practice of permanent or optionally retrievable filter placement for primary prophylaxis in the trauma population is to be supported, further systematic study is required.

Children

Thromboembolic events are less frequent in children than adults. When present, the options for therapy remain the same. The potential for growth and increased life-expectancy for children raises concerns regarding the use of IVC filters. One study has published results of IVC filter placement in 15 children with clinical follow-up. No insertion complications including insertion site thrombosis, no migration, and no filter-related mortality occurred. During follow-up, one patient demonstrated post-thrombotic syndrome symptoms and three patients had common femoral vein reflux, but no recurrent PE occurred.[53] In another study of eight patients; three patients died. The remaining five patients, followed up to 13 months, demonstrated no filter migration, IVC occlusion or thrombosis, or symptomatic pulmonary embolism.[54] From the limited data available, IVC filter placement in children may serve as a useful management tool in patients with a contraindication to anticoagulation. Children do not appear to have an increased risk of complications compared to other study groups.

Septicemia

Infectious complications of IVC filters appear as case reports,[55] but there is a paucity of data regarding this complication. Indeed the single retrospective publication of IVC filter placement in patients with septicemia demonstrated no need for filter retrieval due to infectious complications.[56] Documented 30-day survival was 67%. Filter complications included caval occlusion (1%), recurrent nonfatal PE (1%), recurrent DVT (2.9%), and procedure/deployment complications in 8.6% of patients.[56] Rare case reports of IVC filter infection should not sway the decision to place an IVC filter when clinically indicated in patients with septicemia.

Suprarenal Filter Placement

Suprarenal IVC filter placement may be indicated when the infrarenal IVC size is too large to accommodate a filter (>40 mm), if thrombus in the IVC precludes infrarenal placement, or in cases of filter occlusion or thrombosis. Suprarenal placement historically has been advocated in women who are pregnant or of child-bearing age although there is very little literature to support this practice. Occasionally IVC filters may be required in patients following renal transplant. In this setting even using usual deployment techniques, the IVC filter will be in a suprarenal position. Juxtarenal or suprarenal IVC filter placement may also occur

inadvertently during attempted infrarenal caval filter placement. Concern surrounds suprarenal IVC filter placement due to the risk for IVC thrombosis or thrombus propagation and the potential for fatal renal vein thrombosis. This complication has been seen; however, it appears to be relatively rare.[54,57] From one survey of cancer patients with suprarenal IVC filter placement, two of 13 patients developed renal vein thrombosis.[57]

Greenfield et al. reviewed data on 148 suprarenal IVC filters and compared outcomes to 1932 infrarenal IVC filters placed during the same period.[58] Overall there was no statistically significant difference in the complication rates between the two filter groups. Recurrent PE was documented in 8% and 4% of suprarenal IVC and infrarenal IVC filters, respectively. Caval occlusion was found in 5% of patients. There were no renal complications.[58] Forty-six IVC filters that were inadvertently placed in the suprarenal IVC, juxtarenal IVC, or renal vein were compared to patients with IVC filters.[17] No differences in filter efficacy were identified. PE after filter placement was identified in 7% of patients, but renal complications were not discussed.[17] Although suprarenal IVC filter placement does not appear to be complicated by a preponderance of renal vein thrombosis, in patients with advanced malignancy, a single functioning kidney, chronic kidney disease, or previous renal vein thrombosis, suprarenal IVC filter placement should be avoided if possible.

Superior Vena Cava Filters

Patients with upper extremity DVT who have a contraindication to anticoagulation or experience pulmonary embolism despite adequate anticoagulation have very limited treatment options. SVC filter placement has been studied in this setting.[29,34] In one series, no filter migration, dislodgement, or fracture was identified in 41 patients (median follow-up 12 weeks). No clinical symptoms of SVC syndrome were identified. Central venous catheters or Swan-Ganz catheters were subsequently placed in 56% of patients without complication. One patient had subsequent PE related to left lower extremity DVT.[34] Greenfield et al. reviewed their experience in 72 patients with SVC filter placement. During the index hospitalization, 47% of patients died of causes unrelated to the SVC filter or VTE. No migration was identified by follow-up radiographs. One filter was displaced into the innominate vein by a guidewire during central line placement. No clinical evidence for PE or SVC thrombosis was documented.[29] Upper extremity DVT is not free of typical thromboembolic complications. SVC filter placement may be an alternative form of management in this clinical setting. However, the relative increase in the use of indwelling catheters and transvenous devices such as pacemakers and defibrillators may make permanent deployment of a filter in this position less favorable. Optionally retrievable filters may have a role in this setting, but data are lacking at present.

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C H A P T E R

48

Temporary Filters and Prophylactic Indications

ROBERT B. RUTHERFORD

There has been a four-fold increase in the use of vena cava filters (VCFs) over the last 15 years. It began with the wide availability of percutaneous filter placement using low profile devices and carriers, but this trend has also been associated with a steady increase in the use of prophylactic indications, which now dominate numerically over therapeutic indications. A preceding chapter has dealt with permanent filters, whose indications and results are relatively well established, but recently a number of temporary or retrievable filter devices have been introduced, and their use is also increasing. In certain respects two of these upward trends, in prophylactic indications and the use of retrievable vena cava filters (RVCFs), are linked in that both are most commonly used in dealing with patients who have *not* had a pulmonary embolus (PE) but who are considered to be at high risk of this dreaded complication, yet only for a limited period of time. This chapter will appraise both of these burgeoning practices, and the available evidence regarding these remarkable shifts in the use of VCFs.

THE RATIONALE BEHIND THE USE OF TEMPORARY OR RETRIEVABLE VCFs

The preceding chapter dealt with the complications of vena cava filters, which, it will be seen, provide part of the justification for using temporary or retrievable filters (RVCFs). The justification for using RVCFs is based on two oft-related circumstances: 1) the risk of PE is limited in duration in a number of patient categories and 2) the complications associated with leaving a VCF *in situ* can be significant over time. The latter consideration is particularly pertinent in otherwise healthy younger patients with an extended longevity outlook who would be at risk of these problems for many years.

This was just a theoretical position until a randomized prospective trial suggested that this was indeed the case. The PREPIC trial (*Prevention du Risque d'Embolie Pulmonaire par Interruption Cave*)[1] has been widely quoted as evidence to support the use of temporary/retrievable filters. This trial randomized 400 patients with proximal DVT and a variety of indications for VCF placement into no filter and filter groups, both receiving heparin (contraindication to anticoagulant therapy [AC Rx] was not represented). The choice of filter used was optional and included Vena Tech LGM, Titanium Greenfield, Cardial, or Bird's Nest. After 12 days, there was a significant protection against PE by the filters (1.1% vs. 4.8%, $p = 0.03$) and a very suggestive advantage against fatal PE (0.0% vs. 2.0%, $p = 0.12$). At two years, the protection against PE (3.4% vs. 6.3%, $p = 0.16$) and fatal PE (0.5% vs. 2.5%, $p = 0.21$) appeared to persist, but statistical significance was lost because of diminishing numbers of patients. However, at two years, there was a significantly higher rate of DVT among the filter group (21% vs. 12%, $p = 0.02$). The conclusion was that although filters protected against PE, they carried a higher risk of later DVT. Whether this late DVT risk was related to the thrombogenicity of some of the filters used, and/or associated caval thrombosis due to disturbed flow or intimal changes is not known and the results were not analyzed relative to filter type. Follow-up data at five and eight years[2,3] showed the same trends in terms of DVT, but statistical significance, though close, was lost ($p = 0.06$ at five years and $p = 0.08$ at eight years).

Some have used these late follow-up data to claim that there is not a long-term risk of DVT associated with leaving in VCFs, whereas others have countered that the trends are still clear but that, like many long-term studies, the loss of

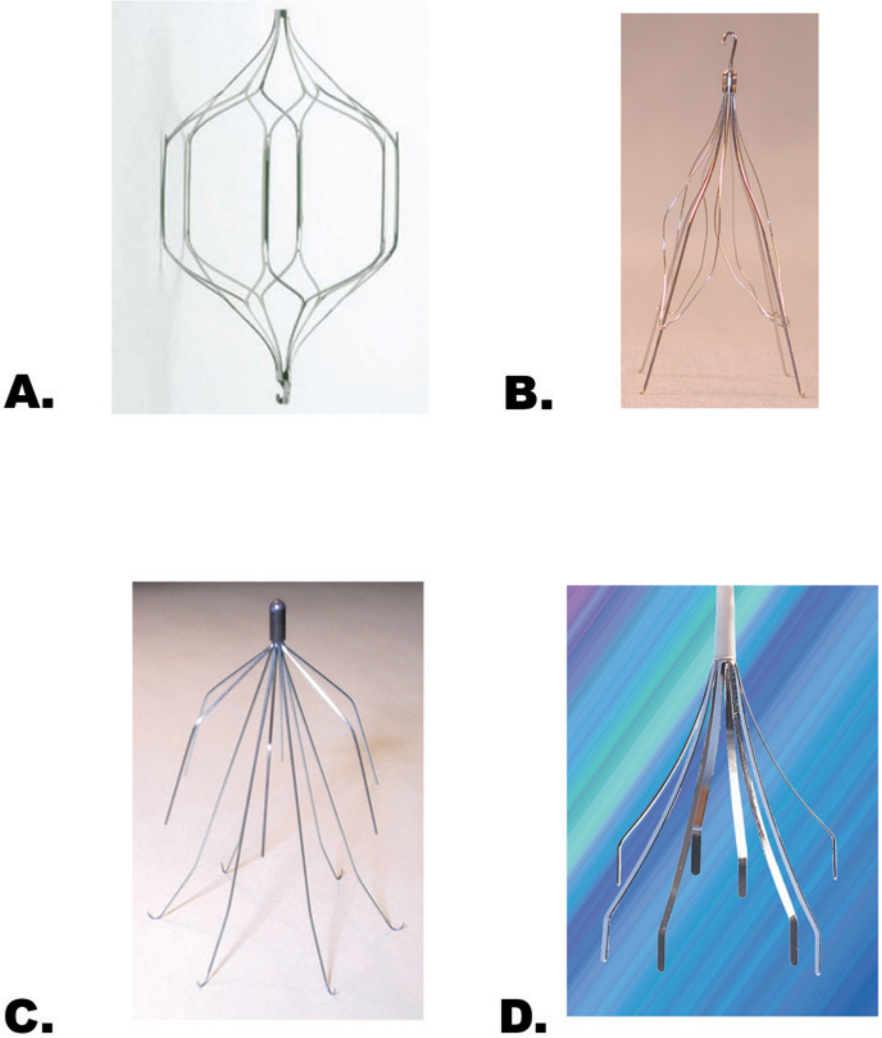

FIGURE 48.1 Four temporary, retrievable IVC filters are shown in a panel **A**. The OptEase (Johnson & Johnson, Cordis Endovascular); **B**. The Gunther Tulip (Cook); **C**. The Recovery (Bard Peripheral Vascular Inc., Tempe Arizona); and **D**. The Tempofilter II (B. Braun, Boulogne, France).

patients to follow-up undermines statistical significance. Nevertheless, this study added great impetus to the development of temporary, retrievable filters for prophylactic indications representing a limited duration of risk of PE.

CURRENTLY AVAILABLE TEMPORARY OR RETRIEVABLE VENA CAVA FILTERS

It is not the purpose of this chapter to compare individual filters. Nevertheless, specific filters will be mentioned in the discussion that follows; therefore they should be identified here. Currently, of the temporary or retrievable filters, the Gunther Tulip (Cook), the OptEase (Cordis), and the Recovery 4 (Bard) have been approved by the FDA in the United States, and the Tempofilter II (Braun), the ALN (ALN filter), and the SafeFlo (Rafael) are available in Europe, under CE Mark, and at least in the case of the former, in Asia and South America as well. The first four of these are shown in Figure 48.1.

PROBLEMS WITH CURRENT RETRIEVABLE VENA CAVA FILTERS

In spite of the impressive technological advances associated with the development of RVCFs, there are still a number of limiting factors that deserve to be pointed out. Removal of many if not most of the current temporary filters becomes increasingly difficult with passage of time because of thrombus in the filter and/or adherence at points of endothelial contact. As a result many have simply been left in. Throm-

bus in a filter can be interpreted as good (a potential PE has been trapped) or bad (device thrombogenicity). This problem in retrieving temporary filters may have resulted in renaming them optional filters, meaning that they can be used as either temporary/retrievable filters or left in as permanent filters. This implies that it is quite permissible (i.e., no significant penalty) to leave them in. This name change may be a marketing ploy because, as of this writing, no good long-term outcome data on these new optional filters has been published to justify leaving them indefinitely (e.g., low rates of recurrent PE, filter migration, filter or caval thrombosis, distal DVT, etc.). The design goal of a filter that optionally can be used either as a temporary filter (i.e., left in longer, as long as the temporary need for protection persists, then safely retrieved) or as a permanent filter (that can be safely left in indefinitely), is a worthy one, but reported experiences suggest that most of the current temporary filters can be left in only a few weeks or months before encountering increasing problems with either contained thrombus or contact point endothelialization, either of which can compromise retrievability. Instructions with some retrievable devices advise removal in 14 or 21 days; others give less specific advice, but two have suggested permissible indwelling times of up to three months. The evidence on this aspect deserves further consideration.

The reported experience with the greatest claim regarding the safe duration before retrieving a temporary VCF has been with the Recovery (Bard) device,[4] which concluded that it "demonstrates the feasibility and safety of retrieval *up to* 134 days after implantation." In 24 of 32 patients (75%), the filters were retrieved between five and 134 days (mean 53 days!). Clot was present in seven (22%), in two large enough to be presumed to be trapped emboli, and presented difficulties with removal. Four patients were alive with their filters still in; three died with filters in place, and in one the filter was removed surgically.

The Tempofilter II (B. Braun) has a similar suggested safe removal time as the Bard Recovery device (i.e., up to three months). Data from a multicenter French study that support this claim has been submitted for publication. This device differs from the others in that introduction and withdrawal is through a tethered catheter with a subcutaneous anchoring device. Thus, leaving it in is not an option but its overall design facilitates the retrieval process.

In a recent report of this approach in multiple trauma victims, by Rosenthal et al.,[5] using the Optease retrievable filter (Cordis Endovascular) and ICU bedside insertion under ultrasound guidance, the filters were successfully placed in 91 of 94 patients, but successfully retrieved in only 31 of 91 (34%) between five to 25 days (mean 19 days). Removal caused a 0.5 cm defect in the caval wall of one patient but without contrast extravasation. Of the 44 filters left in, 41 were not removed "because of the severity of the injury prevented—initiation of—anticoagulation prophylaxis," but three were left in because of trapped thrombi. One patient had a PE after filter removal.

One makeshift solution to this problem has been to reposition the filter every 12 to 14 days. Offner et al.[6] reported repositioning the filter every 12 days if it was not ready to be retrieved. But this was done in less than one-quarter (9/44) of patients, and in three patients the filter could not be removed because of either trapped clot (n = 2) or angulation (one case).

A Spanish experience with the Gunther Tulip[7] also reported repositioning as a way of achieving a longer indwelling time than the recommended 14 days. They used this strategy in 26% of 87 patients. Seventy of 88 filters (almost 80%) eventually had their filters removed. The mean indwelling time was 34.8 days; the average number of repositionings was 1.5, and the mean repositioning interval 13.8 days. Eighteen patients had their VCFs left in permanently: in one, fixation in the IVC prevented removal at 16 days; two were left in because of large entrapped thrombus; and all had "varying amounts of fibrous and fibrotic material adhering to the filter struts." Focal tears, associated with intramural hematomas as large as 10 mm in diameter, were visualized angiographically after filter removal, but there were no transmural lacerations or contrast extravasations.

Finally, it should be pointed out that each intervention to change filter position or retrieve the VCF is, to a degree, invasive and presents some risk of patient harm. These retrieval procedures represent an additional cost ($3000–$5000), which is not currently reimbursed in the United States.[8] This begs the issue: if there is a permanent filter that can be left in for long periods of time without significant penalty, why not use it rather than a retrievable VCF? The results of the PREPIC trial were not stratified for the different permanent filters used (some of which may have been described in the previous two chapters). Nevertheless, one of the de-vices used, the Titanium Greenfield filter, was a low-profile version of the original stainless steel Greenfield filter, which has reported excellent 12- and 20-year results in terms of recurrent PE, caval patency, and DVT,[9,10] and which has since been supplemented by an over-the-wire stainless steel Greenfield. Both of these low-profile, permanent filters appear to mimic the performance of their predecessor.[11,12] Pending the correction of existing problems with current RVCFs, an alternative strategy then is to use permanent filters even for prophylactic reasons, which is currently the majority practice. The duration of safe indwelling time was recognized as a significant limitation of temporary filters in a survey of North American and European practices conducted by B. Braun, being identified as a major issue by 40% of those using RVCFs, and the majority of those continuing to use only permanent filters gave this as a major reason (B. Braun, personal communication). A minor objection to persisting with this approach is that there is a small

but definite need, even in the best permanent filter, for repositioning or retrieval on occasion.

So, in summary, many if not most of the current temporary filters develop progressive problems with entrapped thrombus and endothelial incorporation with time, sufficient to compromising their retrievability. The safe removal time recommended by the manufacturer for different devices varies from three weeks to three months but is not well documented by reported data. Early removal of the device because of these limitations has resulted in PEs occurring *after* removal. Repositioning, to extend the safe indwelling time, has met with only limited success. Further design modifications may well be needed to extend the reliable time for *completely* safe removal. If this were extended to somewhere between six weeks and three months it would greatly widen RVCF application. As matters stand, retrievable RVCFs have not replaced permanent VCFs, even for prophylactic indications.

PROPHYLACTIC INDICATIONS: CRITICAL APPRAISAL

The major and steady increases in the use of prophylactic indications over the last three or four decades, to the point where it clearly dominates over therapeutic indications, have a number of likely reasons, but because all the conditions for which VCFs are being applied were all present by the time effective permanent VCFs were available, in the late 1960s, it seems appropriate to question the justification for such a large increase, particularly since there does not appear to be good data-based evidence for most prophylactic indications. Some general statements can be made about prophylactic indications in some respects but in other respects, it is necessary to focus on individual categorical prophylactic indications to pinpoint key issues.

CHANGES IN REFERRAL PATTERNS AND SPECIALIST PERFORMING THE PROCEDURE

The placement of VCFs, in the period after well-designed permanent devices were developed and available, was performed through remote cut-down under general or local anesthesia with sedation, with a then-acceptably low procedural morbidity and mortality, the latter usually being attributable to intercurrent disease rather than operative misadventures. What percutaneous placement of the newer low-profile devices offered was the avoidance of open surgery, empirically attractive to referring physicians. Although vascular surgeons continued to participate in these trends and introduce new technology and technical approaches, percutaneous placement increasingly opened the door to other interventionalists (e.g., an interventional radiologist, cardiologist, or other specialist with catheter skills). In addition, the referring physicians more often were those without a primary interest in the management of VTE and AC therapy (e.g., an oncologist, trauma surgeon, bariatric surgeon, orthopedic surgeon, neurosurgeon). This combination of less knowledgeable, less critical physician referrals and ready acceptance by service-oriented interventionalists may have played a major role in liberalizing the indications for prophylactic VCF use.

LACK OF ADEQUATE EVIDENCE ON WHICH TO BASE DECISIONS REGARDING VCF USE

These changing referring physician-interventionalist arrangements may not only have resulted in an apparent lack of critical appraisal of expanding indications but a dearth of critical outcome assessments. In a Medline search of 568 references from 1975 to 2000 on VCFs, Girard et al.[13] found that 65% either were retrospective studies (33.3%) or case reports (31.7%), that 12.9% were animal or *in vitro* experiments, and only 7.4% were prospective studies. Only 16 studies involved more than 100 cases and there was only one randomized study. In contrast, 47.4% of 531 references on heparin in VTE were randomized prospective trials. This is a striking contrast and should serve as a challenge to those involved with VCF placement to come up with higher level data on which to base current practice.

ISSUES WITH INDIVIDUAL PROPHYLACTIC INDICATIONS

Each prophylactic indication category deserves individual comment in terms of VCF use.

Multiple Trauma

Multiple long bone fractures, severe closed head injuries, vertebral spine injuries with and without cord injury, pelvic or acetabular fractures, associated major direct venous trauma, and essentially any other multiple system trauma predicted to require extended period of immobilization are generally considered to be reasonable prophylactic indications for inserting a VCF, but each subgroup deserves clearer definition. Severe, multisystem trauma is associated with periods of hypercoagulability, and in some instances, involves direct or indirect venous trauma or endothelial damage. These types of trauma are known to be associated with a high risk of VTE and AC Rx is usually contraindicated. Intermittent pneumatic compression (IPC) and/or

duplex surveillance (DS) is another prophylactic measure to be considered, and IVC filter placement is appropriate only when this is not practical or deemed effective. It is important to note that these patients need protection only until they are ambulatory or AC therapy can be instituted.

Although the justification for temporary caval filtration relates to the limited duration of the need for protection, it is spurred by the fact that most trauma patients are young and their expected longevity is great relative to the duration of this need. Nevertheless, the duration of risk may be quite long in many of these types of trauma relative to the safe indwelling time of most current retrievable filters. In such cases, with predictably long immobilization (e.g., spinal fractures, pelvic fractures, multiple long bone fractures), it might be better to use a permanent filter, the one with the best long-term performance record.

VCFs have been reported to be effective for this category of prophylactic use. Langhan et al.[14] reported a 99.5% effectiveness but also reported a 12.8% rate of DVT, after filter insertion, with an additional 10.3% in those followed later. However, only 47% returned for follow-up (a problem with trauma patients), and the filter was visualized in only 52% of those. On a survey questionnaire of the others, 27 had leg swelling, 14 had other extremity symptoms, nine had shortness of breath, seven had chest pain, and four had venous skin changes. It cannot be determined, from such a follow-up, how many of these reported problems could have reflected VTE. There were three nonfatal filter complications, but all 27 deaths were attributed to the trauma, not the VCF. Clearly, the protection against PE was excellent but, much like the PREPIC trial,[1] there appears to be a penalty for this approach in the form of DVT.

In a more recent report of this approach in multiple trauma victims, Rosenthal et al.[5] reported that the filters were successfully placed with 96.8% technical success. None of the 19 deaths was reportedly from VCF placement, and there were complications in only 5.3%. One patient had a PE after filter removal. Follow-up in this study was short and the incidence of DVT was not documented. In another evaluation of this approach from a trauma center, Duperier et al.[15] reported a low rate of insertion complications in 133 consecutive multiple trauma patients, but "DVT was observed in 30% of patients despite 92% being on prophylaxis"; 26% were *de novo*. In this experience, the filter was inserted an average of 6.8 +/− 0.6 (SE) days after trauma. In the previously cited experience of Langhan,[14] the mean insertion day was 6. This delay in insertion of the VCF in earlier trauma experiences, before the practice of bedside filter insertion under ultrasound guidance, reinforces the potential value of this relatively recent capability.

One critical appraisal of the prophylactic use of VCFs in trauma patients has been recently been reported by Knudsen et al.[16] In an analysis of 1,602 episodes of VTE from the American College of Surgeons National Trauma Data Bank, they observed that 90% had at least one of nine accepted risk factors, and found the following factors correlated significantly with outcome: age (>40), lower extremity fracture, a high trauma score, head injury, prolonged ventilator support (> three days), venous injury, and major operative procedure. Eighty-six percent had prophylactic IVC filters placed, but 11% had no identifiable risk factors. They concluded that 1) patients who need VTE prophylaxis after trauma can be identified by risk factors and 2) the use of prophylactic IVC filters in trauma patients should be reexamined.

Patients with Neurological Problems Resulting in Paralysis or Prolonged Immobilization

Paralyzed or otherwise immobilized patients are at high risk for VTE, but many can be managed by anticoagulant therapy. In those in whom anticoagulants are contraindicated, if the limbs are accessible (i.e., not injured or encumbered), intermittent pneumatic compression (IPC) and duplex surveillance (DS) can be used, and may be effective. There are, however, patients in whom AC therapy is contraindicated or in whom the limbs are not accessible for IPC or DS (e.g., closed head or acute cord injuries associated with long bone fractures) in which VCFs may be justified. Outside of this exemplary exception, other forms of prophylaxis probably should be used with some form of surveillance for DVT added.

Two recent articles attest to this generic advice. Maxwell et al.[17] studied 111 spinal cord–injured patients from a registry of 8,269 trauma admissions, and found that using these other means of prophylaxis, there was an overall incidence of DVT and PE of 9.0% and 1.8%, respectively, but with no deaths. Mean hospital stay was 23 days and DS was performed an average of 2.3 +/− 2.1 times. The incidence of DVT and PE with low molecular weight (LMW) heparin alone was 11.1% and 2.8%, respectively, but when this was combined with DS, it was only 7.4% and 0%, respectively, so the latter combination was recommended. By comparison, in a subgroup with long bone fractures, the incidence of DVT was 37.5%. They concluded that IVC filters were needed only in spinal cord injury patients with associated long bone fractures, in those with detected DVT or its progression under surveillance, or when AC therapy was contraindicated.

This agrees with guidelines developed by a committee of neurosurgeons[18] who agreed that low-dose LMW heparin alone is insufficient and recommended rotating beds, IPC, and DS in addition, with VCF inserted only if DVT was detected. Thus, recent opinion appears to suggest that the role of VCFs in this category should be limited to those who develop DVT despite other forms of prophylaxis.

Patients with Advanced Malignancy

Patients with advanced malignancy have been shown to be at increased risk of VTE, and AC therapy may not be adequately protective. Prophylactic VCF use has been debated but the trend now favors therapeutic use (i.e., only after VTE). Risk factors have been identified.[19] Univariate analysis and logistic regression models identified the following as significant risk factors for recurrent VTE: the appearance of new metastases, a history of DVT, and neutropenia as a result of chemotherapy. Other studies have identified stage of disease and type of malignancy as specific risk factors for VTE. The effectiveness of VCFs in preventing PE has not in itself been challenged, but use of this indication for VCF placement clearly must be balanced by patient prognosis as demonstrated by two sobering reports. Jarrett et al.[20] reported on 116 patients with VCFs placed for advanced malignant disease. Its effectiveness was suggested by the fact that two had recurrent DVT, three had PE after VCF, but it was the issue of patient survival that was challenged. Life table analysis showed survival to be 68% at 30 days, 49.4% at three months, and 26.8% at one year. Of those with stage IV disease, 46% died within six weeks and only 13.7% were alive at one year. Schunn et al.[21] reported 97.5% protection against PE in 40 patients with advanced malignancy receiving VCFs, but also a high (20%) complication rate. Added to this, 30% survived less than 30 days! It can be concluded from these experiences that prevention of PE may be of little benefit in patients with advanced (e.g., stage IV) disease due to short life expectancy.

Major Surgery Associated with a High Risk of DVT

Certain categories of major surgery have a predicted high VTE risk, and yet the use of AC prophylaxis may be contraindicated or presumed ineffective. In such patients, VCF has been felt to be indicated. Some well-known examples of such VCF use include pelvic surgery, hip surgery, major surgery with history of DVT, major surgery with known or suspected hypercoagulable state, major venous reconstructions with VTE risk, and gastric bypass surgery for morbid obesity. As a general criticism, in many of these applications, the risk of VTE, the duration of risk, and the benefits of VCFs are poorly documented in the literature, and few studies involve valid comparisons with alternative methods of prophylaxis. Nevertheless, it is clear that individual high-risk patients can be identified, and when alternative methods of prophylaxis are either contraindicated or ineffective, VCF placement should be considered. As a general rule, in this subcategory, a temporary/retrievable filter should be used if the patient can be ambulatory or AC therapy can be instituted in about three weeks, otherwise a permanent filter may be preferable. Thus, although supporting data are scant, individual high-risk patients can be reasonably chosen on their own merits, and it is difficult to take exception with this practice.

Bariatric surgery has received much recent attention, and though the intervention itself has been challenged by many, some data and guidelines have emerged for prophylactic VCF use with this operation. Open gastric bypass for morbid obesity carries a 1 to 4% PE risk in spite of other methods of prophylaxis including IC, LMW heparin, and a push for early ambulation. Using retrievable VCFs, Gargiulo[22] reported a reduced PE rate in open gastric bypass for patients with a BMI >55, but there was 14% complication rate. Factors associated with a high risk of VTE have been identified[23] to include BMI >60, truncal obesity, venous stasis dermatitis, and hypoventilation/sleep apnea syndrome. Logically, one would add those with a history of VTE and a known or probable hypercoagulable state. It has been said that this operation has a short, defined period of risk for VTE that is ideal for retrievable VCFs. On the other hand, VCF placement can be challenging in morbidly obese patients, especially the super-obese (BMI >60). Duplex ultrasound guidance is impossible but intravascular ultrasound can be used to advantage in placing a filter in these patients. In the face of great enthusiasm for this indication for prophylactic VCF use, the author would insert a word of caution: no prospective studies, comparing VCFs with alternative methods of VTE prophylaxis, have been carried out, and most of the published reports related to its use have dealt with open gastric bypass. It is quite conceivable that the laparoscopic approach, with its earlier ambulation, may significantly reduce the VTE risk. Whether this is sufficient to allow the adjunctive use of IPC and LMW heparin to be effective deserves investigation. In the meantime, the risk factors listed earlier should serve as guidelines for selective VCF use.

SUMMARY AND CONCLUSIONS

The current use of prophylactic indications for caval filter placement and the temporary retrievable filters that have been developed for this purpose has been reviewed. Based on this some recommendations can be confidently made, but there is a clear need better information, clarifying higher level studies on which to base prophylactic indications. Also, there appears to room for further improvements in retrievable vena cava filter design, or possibly the modification of an existing permanent filter with good long-term outcomes so that it can be retrieved if necessary. It may or may not be possible to design a truly optional filter, one that can be retrieved as needed or left in permanently without penalty. If not, the use of two types of filters will persist as the best strategy—the best temporary/retrievable and best permanent filter being chosen matching duration of patient

risk with safe indwelling time in the former. Better supporting data are required to support either use. It is also apparent that, in respect to categories of prophylactic indications, current practice is not based on a high level of medical evidence and, in fact, the use of VCFs in some of these settings appears to be excessive and subjectively determined. It is hoped that prophylactic indications within each subcategory will be refined in the future by indication-specific prospective analyses of critical outcome data compared with alternative methods of prophylaxis, and that these studies also will identify the factors significantly affecting outcome as a basis for more objective guidelines for application. The need for evidence-based medicine here is obvious. Industry-driven trials of single devices are not, in themselves, acceptable for this purpose and tend to promote excessive prophylactic use rather than control it. On the other hand, if one believes, as does the author, in the potential of new technology in bringing about continuing improvements, industry can be expected to develop even better retrievable caval filters, those which ultimately could be proven safe and effective for prophylactic use in patients temporarily at high risk for VTE, specifically filters that can be retrieved or repositioned safely, without being compromised by entrapped clot or contact point endothelialization for longer periods of time relative to the risk of VTE. Until then, it is hoped that this critical appraisal of the prophylactic use of VCFs, and the current temporary filters that increasingly are linked to it, will help guide physicians engaged in this practice.

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CHAPTER

49

Thrombolytic Therapy for Acute Venous Thrombosis

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INTRODUCTION

Despite evidence demonstrating that patients with iliofemoral venous thrombosis suffer more severe postthrombotic sequelae than patients with infrainguinal deep venous thrombosis (DVT), the majority of physicians treat all patients with acute DVT with anticoagulation alone. A treatment approach that includes a strategy of thrombus removal and optimal anticoagulation is not adopted by most clinicians, even in patients with extensive venous thrombosis.

Unquestionably, there have been enormous advances in anticoagulation. Anticoagulants, such as low-molecular-weight heparins (LMWH) and pentasaccharides, and other families of agents, such as the direct thrombin inhibitors, serve to limit progression of thrombosis and, with proper duration of therapy, prevent recurrences; however, they are not designed to clear thrombus from the deep venous system.

It appears that patients with iliofemoral DVT are a clinically relevant subset of patients with acute DVT who suffer severe postthrombotic morbidity.[1–3] O'Donnell and colleagues[1] were among the first to bring to our attention the high incidence of postthrombotic venous ulceration, the large number of recurrent hospitalizations, and the loss in financial productivity in these patients. Akesson et al.[2] showed that 95% of patients with iliofemoral DVT treated with anticoagulation alone had ambulatory venous hypertension at five years, and 90% suffered symptoms of chronic venous insufficiency. During this relatively short follow-up, 15% of patients already developed venous ulceration and another 15% had debilitating symptoms of venous claudication. Delis et al.[3] demonstrated that venous claudication occurred in 40% of patients with iliofemoral DVT treated with anticoagulation when they were studied with exercise testing.

UNDERSTANDING POSTTHROMBOTIC VENOUS INSUFFICIENCY

Many physicians fail to recognize the difference in the pathophysiology of primary versus postthrombotic venous insufficiency. As a result, the value of thrombus removal in preventing postthrombotic morbidity in patients with acute DVT is underestimated. The pathophysiology of chronic venous insufficiency is ambulatory venous hypertension, which is defined as an elevated venous pressure during exercise. In individuals with a normal deep venous system, ambulatory venous pressures in the lower leg and foot should drop to less than 50% of the standing venous pressure. In patients with postthrombotic syndrome, the ambulatory venous pressure drops very little, and in those with persistent proximal venous occlusion, the ambulatory pressures may actually rise above standing pressure. This degree of ambulatory venous hypertension often leads to the debilitating symptoms of venous claudication.

The anatomic components contributing to ambulatory venous hypertension are venous valvular incompetence and luminal obstruction. It has been consistently shown that the most severe postthrombotic sequelae and the highest ambulatory venous pressures occur in patients with valvular incompetence accompanied by luminal venous obstruction.[4,5]

Venous obstruction is not synonymous with occlusion. Occlusion is complete obliteration whereas obstruction (for the most part) is relative narrowing of the lumen. Although relative degrees of obstruction are reliably quantitated on the arterial side of the circulation, technology has not advanced to the point that allows this degree of accuracy on the venous side. Furthermore, physicians often cannot put venous obstruction into proper perspective pathophysiologically in

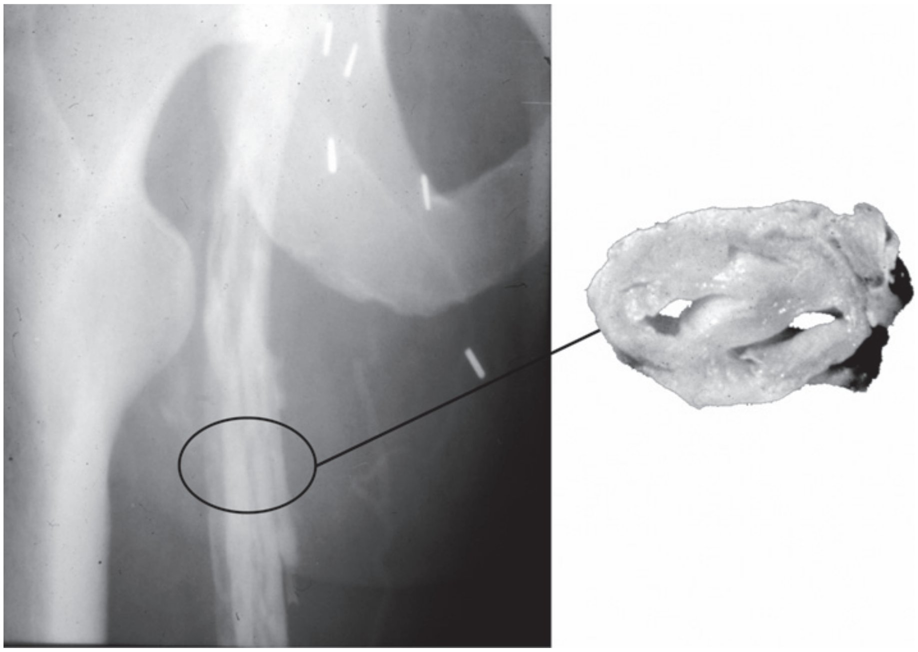

FIGURE 49.1 Chronic venous disease in a patient who had iliofemoral DVT 10 years earlier. The patient suffered with the postthrombotic syndrome leading to multiple hospitalizations due to venous ulcers. Ascending phlebography showed chronic venous disease with "no evidence of obstruction." An IPG was normal. A classic Linton procedure, which includes ligation of the femoral vein distal to its junction with the profunda, was performed, showing recanalization of the femoral vein with significant luminal obstruction.

terms of its contribution to postthrombotic discomfort or distal leg soft tissue damage. Our ability to identify and quantitate venous obstruction is so poor that there is widespread underappreciation regarding the importance of the contribution of obstruction to postthrombotic morbidity.

Unfortunately, physiologic testing on the venous side of the circulation has not kept pace with similar advances on the arterial side of the vascular tree. Vascular laboratories have traditionally (and paradoxically) tested the hemodynamics of venous obstruction with patients in the resting, supine position with their legs elevated, which is the standard position for measuring maximum venous outflow, the commonly accepted test for venous obstruction. However, the pathophysiology of chronic venous disease is defined in the upright, exercising patient, with increased arterial inflow stressing venous return. Phlebograms of postthrombotic recanalized veins frequently document patency, and noninvasive studies may indeed show normal maximal venous outflow values, giving the mistaken impression that venous obstruction contributes little to postthrombotic morbidity.

This is clearly illustrated by the patient represented in Figure 49.1, who had iliofemoral DVT 10 years earlier and was suffering with severe postthrombotic syndrome and a venous ulcer. Noninvasive testing demonstrated that the patient had valvular incompetence but a normal three-second maximal venous outflow. An ascending phlebogram was interpreted as "the classic tree-barking appearance of chronic venous disease. There is no evidence of venous obstruction." The following day the patient underwent a classic Linton procedure, which included femoral vein ligation with division just below its junction with the profunda femoris vein. A cross-section of the divided femoral vein is shown in Figure 49.1, along with its corresponding level on the ascending phlebogram. The vein shows multiple recanalization channels and substantial luminal obstruction. This severity of luminal obstruction becomes hemodynamically important in the exercising limb, in which substantial increases in arterial flow occur as a result of exercise. With exercise, venous outflow becomes restricted by the luminal obstruction, significantly contributing to ambulatory venous hypertension. Of course, the valves within these diseased veins are destroyed, and patients also have valvular incompetence.

It makes intuitive sense that eliminating the acute thrombus leading to the persistent venous obstruction would benefit patients over the long term, and indeed it does. Furthermore, thrombus extraction not only eliminates venous obstruction but also preserves valvular function.

BENEFITS OF THROMBUS REMOVAL

There is increasing evidence that thrombus removal or early thrombus resolution after acute DVT is associated with improved outcomes. Benefits of thrombus removal derive from data generated from experimental animal studies, findings from natural history studies of acute DVT treated with anticoagulation, venous thrombectomy data, and observations following systemic and catheter-directed thrombolysis.

Cho and colleagues[6] and Rhodes and associates[7] have used a canine experimental model of acute DVT to compare the results of thrombolysis versus placebo and mechanical thrombectomy. They demonstrated that thrombolysis with urokinase preserves endothelial function and valve competence, both immediately and at four weeks after therapy. There was less residual thrombus in veins treated with urokinase, thereby preserving the vein's structural integrity.

The aforementioned experimental observations translated into clinical outcome when the University of Washington investigators performed a natural history study of acute DVT treated with anticoagulation.[8–11] This NIH-supported effort resulted in observations indicating that persistent obstruction of proximal veins was associated with distal valve incompetence. The combination of venous obstruction and valve incompetence was associated with the most severe postthrombotic morbidity. Spontaneous clot lysis naturally restored venous patency. If spontaneous lysis occurred early (within 90 days), valve function was frequently preserved.

The initial trials of thrombolytic therapy for acute DVT involved systemic administration of the plasminogen activators. The cumulative results of these trials demonstrated that although 45% of patients had substantial or complete lysis, the majority did not.[12] Those whose clot was successfully lysed had a significant reduction in postthrombotic morbidity and preservation of venous valve function. Goldhaber et al.[13] reviewed the results from eight trials of systemic streptokinase treatment for acute DVT and found that moderate or significant thrombolysis was achieved almost three times more frequently among patients treated with thrombolytic therapy than among patients treated with anticoagulation alone. However, there was nearly a fourfold increased risk of major bleeding in those receiving thrombolytic therapy, thereby focusing the attention of clinicians on the hemorrhagic morbidity of lytics rather than their potential for long-term benefit.

The long-term efficacy of thrombus removal in patients with acute iliofemoral DVT was further substantiated by the Scandinavian investigators who performed a randomized trial of iliofemoral venous thrombectomy with an arteriovenous fistula (AVF) and anticoagulation versus anticoagulation alone.[14–16] Follow-up at six months, five years, and 10 years demonstrated clear benefit in patients randomized to venous thrombectomy. Early thrombus removal resulted in improved patency of the iliofemoral venous system, lower venous pressures, less edema, and fewer postthrombotic symptoms.

These observations, extending from the basic research laboratory through systemic thrombolysis and operative venous thrombectomy, support the concept that thrombus removal in patients with acute iliofemoral DVT results in significantly less postthrombotic morbidity. Unfortunately, the favorable results of contemporary venous thrombectomy have not led to much enthusiasm for the operative procedure in the United States. Additionally, physicians are unwilling to accept the higher risk of bleeding complications with lytic therapy; therefore, systemic thrombolysis for acute DVT is infrequently used and not recommended, which is appropriate in light of the improved results with catheter-directed lysis.

INTRATHROMBUS CATHETER-DIRECTED THROMBOLYSIS

Rationale

The mechanism by which thrombolysis results in clot dissolution is the activation of fibrin-bound plasminogen.[17] When circulating GLU-plasminogen binds to fibrin, it is modified to LYS-plasminogen, which has greater affinity for plasminogen activators. When delivered into the thrombus, a plasminogen activator efficiently activates LYS-plasminogen. The intrathrombus delivery protects the plasminogen activator from neutralization by circulating plasminogen activator inhibitors and also protects the resultant plasmin from neutralization by circulating alpha 2-antiplasmins.

Catheter-directed techniques that deliver the plasminogen activator into the thrombus theoretically can accelerate thrombolysis, which increases the likelihood of a successful outcome. By reducing the overall dose and duration of infusion of the plasminogen activator, it is reasonable that complications will be minimized.

Results

Numerous reports have emerged supporting favorable outcomes of catheter-directed thrombolysis for acute DVT.[18–25] Three of the larger reports demonstrate approximately an 80% success rate (see Table 49.1). Initial success rates might have been higher had treatment been restricted to only patients with acute iliofemoral DVT. However, patients who had more distal and chronic venous thrombosis were included, resulting in a lower overall success rate. In these three studies, 422 patients were treated with remarkably consistent rates of success and complications.[18–20]

TABLE 49.1 Results of Catheter-Directed Thrombolysis with Urokinase in Three Contemporary Series: Efficacy and Complications

Efficacy	**Bjarnason et al.[18] (n = 77)**	**Mewissen et al.[19] (n = 287)**	**Comerota et al.[20] (n = 58)**
Initial Success	79%	83%	84%
Iliac	63%	64%	78%
Femoral	40%	47%	—
Primary Patency at 1 yr			
Iliac	63%	64%	78%
Femoral	40%	47%	—
Iliac Stent: Patency at 1 yr			
+Stent	54%	74%	89%
–Stent	75%	53%	71%
Complications			
Major Bleed	5%	11%	9%
Intracranial Bleeding	0%	<1%	0%
Pulmonary Embolism	1%	1%	0%
Fatal Pulmonary Embolism	0%	0.2%	0%
Death Secondary to Lysis	0%	0.4%	0% (? 2%)*

*Death due to multiorgan system failure 30 days post lysis, though not related to lytic therapy.

Catheter-directed urokinase was used in each of these studies. Underlying iliac vein stenoses were treated with balloon angioplasty, stenting, or both to achieve unobstructed venous drainage into the vena cava and reduce the risk of recurrent thrombosis (see Figure 49.2).

Major bleeding occurred in 5 to 10% of cases, with the majority resulting from puncture site bleeding. Intracranial bleeding was rare, occurring in only three patients in the National Venous Registry.[19] This resulted in the death of one patient. Pulmonary embolism (PE) occurred in 1% of patients in the series reported by Bjarnason et al.[18] and the National Venous Registry, and fatal PE occurred in only one out of the 422 patients. Therefore, death as a result of catheter-directed thrombolysis was rare.

Until approximately six years ago, most patients treated with catheter-directed thrombolysis were managed with urokinase. Since urokinase was removed from the market, catheter-directed alteplase and reteplase have demonstrated similarly good results.[22–25]

An interesting new therapeutic approach was reported by Chang et al.[23] when they used intrathrombus bolus dosing of rt-PA in 12 lower extremities of 10 patients with acute DVT. They infused rt-PA intrathrombus using the pulse-spray technique and no more than 50 mg per treatment. After the pulse-spray bolus, patients were returned to their rooms and brought back the following day for repeat venographic examination. Continuous infusion was not used. Patients had treatment repeated for up to four daily sessions. Results were excellent; 11 lower extremities had significant or complete lysis, and the remaining leg had 50 to 75% lysis. Although the average total dose of rt-PA was 106 mg, bleeding complications were minor and no patient had a decrease in hematocrit more than 2%. This technique is deserving of further study to evaluate whether others can obtain similarly good results.

A further analysis of the patients treated in the National Venous Registry[19] offers important clinical insight into catheter-directed thrombolysis for patients with acute DVT. Of the 287 patients treated in both academic and community centers, 66% had acute DVT, 16% had chronic DVT, and 19% had an acute episode superimposed upon a chronic condition. Seventy-one percent of the patients presented with iliofemoral DVT and 25% with femoropopliteal DVT. Catheter-directed thrombolysis with intrathrombus infusion of urokinase was the preferred approach. However, some patients were treated with urokinase infused into a foot vein, which was essentially systemic thrombolysis. Phlebographic evaluation showed that 31% of patients had complete lytic success and 52% had 50 to 99% lytic success. In 17% of patients, less than 50% of the thrombus was dissolved. When urokinase was not infused intrathrombus, success rates fell dramatically. In the subgroup of patients with acute, first-time iliofemoral DVT, 65% of the patients enjoyed complete clot lysis.

During follow-up, thrombosis-free survival was observed in 65% at six months and in 60% at 12 months. There was a significant correlation ($P < .001$) of thrombosis-free survival with the results of initial therapy. Seventy-eight percent of patients with complete clot resolution had patent veins at one year, compared with only 37% of those in whom less than 50% of the clot was dissolved. Interestingly, in the subgroup of patients with acute, first-time iliofemoral DVT who had successful thrombolysis, 96% of the veins remained patent at one year. In addition to sustained patency, early success directly correlated with valve function at six months. Sixty-two percent of patients with less than 50% thrombolysis had venous valvular incompetence, whereas 72% of patients who had complete lysis had normal valve function ($P < .02$).

The large database of the National Venous Registry offered an opportunity to objectively evaluate the long-term impact of catheter-directed thrombolysis on patients with iliofemoral DVT. Since the National Venous Registry collected data only on patients treated with thrombolytic therapy, a contemporary cohort of patients with iliofemoral DVT treated with anticoagulation in the same institutions was identified. All anticoagulated patients were candidates for lytic therapy but were treated with anticoagulation alone due to physician preference. A validated quality-of-life (QOL) questionnaire was used to query patients at 16 and 22 months posttreatment. Of the 98 patients studied, 68 were treated with catheter-directed lysis and 30 treated with anticoagulation alone. Those treated with catheter-directed

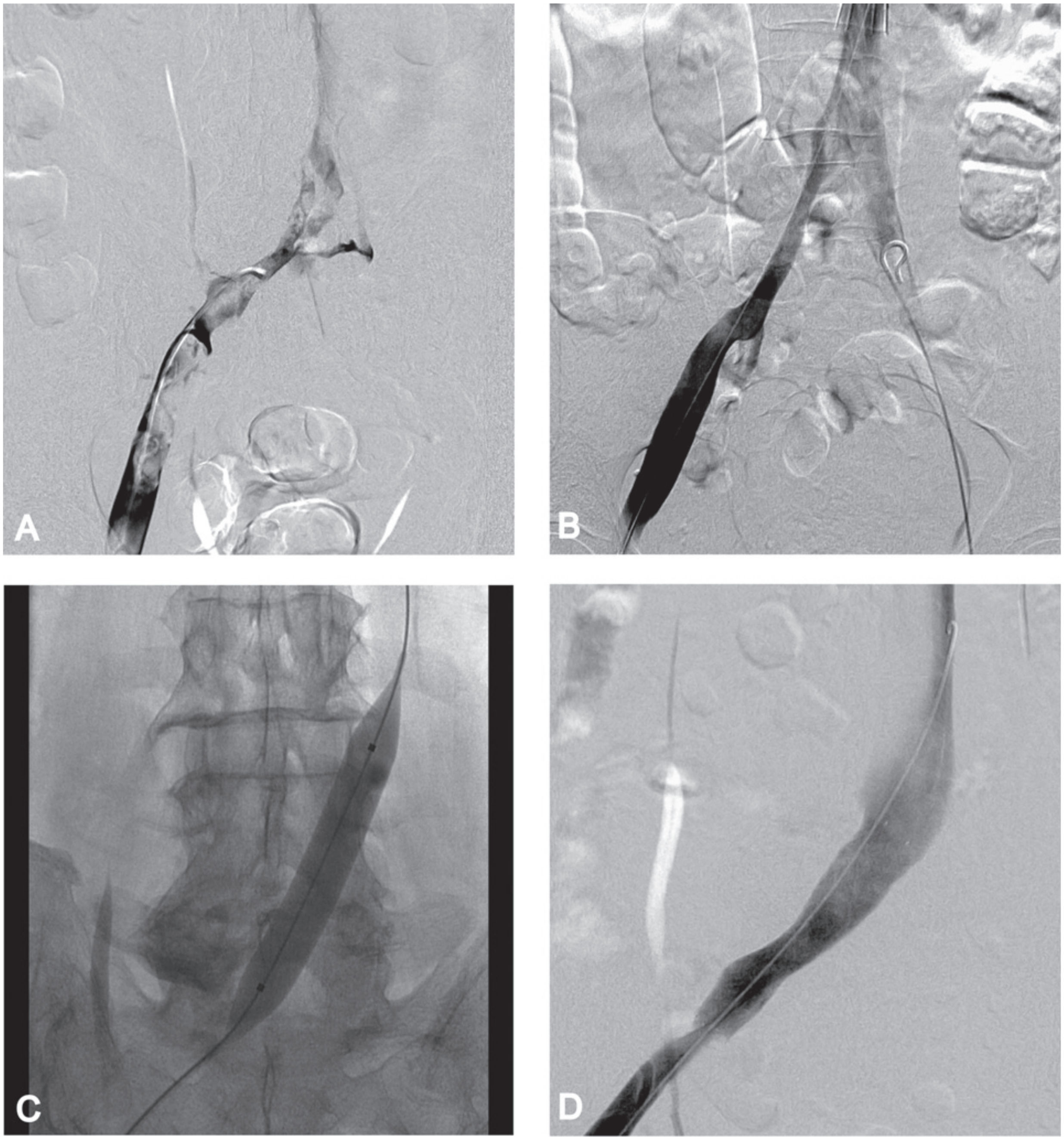

FIGURE 49.2 **A**. Initial phlebogram (prone iliocavagram) of a patient with extensive iliofemoral DVT who presented with a swollen, painful left leg. Using ultrasound guidance, the catheter was positioned into the thrombus of the iliofemoral segment. A plasminogen activator (t-PA) was infused at 1 mg/hr. **B**. After 22 hours of catheter-directed t-PA infusion, the patient had a good phlebographic and clinical response. A stenosis of the left iliac vein was identified. **C**. The stenosis was treated with balloon angioplasty and a 16-mm Wallstent was deployed and dilated. **D**. Final phlebogram showing unobstructed venous drainage into the vena cava.

thrombolysis reported a significantly better QOL than those treated with anticoagulation alone. The QOL results were directly related to the initial success of thrombolysis. Patients who had a successful lytic outcome reported a significantly better Health Utilities Index, better physical functioning, less stigma of chronic venous disease, less health distress, and fewer overall postthrombotic symptoms. Patients in whom catheter-directed thrombolysis failed had similar outcomes to patients treated with anticoagulation alone. These efficacy data combined with the observed reduction in

complications offer a sound argument for the management of patients with iliofemoral DVT with catheter-directed thrombolysis.

A small, randomized trial performed by Elsharawy et al.[26] demonstrated that catheter-directed thrombolysis versus anticoagulation alone offered significantly better outcomes at six months. Assuming patients are properly managed with anticoagulation, the six-month observations should reflect their long-term outcome.

We believe that the results available to date support a strategy of catheter-directed thrombolysis for acute iliofemoral DVT in patients who have no contraindication to thrombolytic therapy. If a contraindication to lytic therapy exists, a contemporary venous thrombectomy (Chapter 45) followed by long-term anticoagulation should be considered.

PATIENT EVALUATION AND TECHNIQUE OF CATHETER-DIRECTED THROMBOLYSIS

Patient Evaluation

It is intuitive and clinically apparent that patients with iliofemoral DVT have a greater stimulus to thrombosis than the majority of patients with DVT and therefore warrant a search for an underlying etiology. Asymptomatic pulmonary emboli are present in at least 50%. It is important that the PE be recognized early, since up to 25% will subsequently become symptomatic, manifesting as pleuritic chest discomfort once the inflammatory pulmonary process reaches the pleural surface. If the PE is not recognized, the clinician often mistakenly assumes that the pleuritic symptoms are due to a new PE and failure of treatment. A spiral CT scan of the chest with contrast evaluates the pulmonary vasculature for PE and other thoracic pathology (see Figure 49.3a). The CT is extended to the abdomen and pelvis to identify the proximal extent of thrombus and to evaluate for abdominal or pelvic pathology (see Figure 49.3b). This has been an important addition to the evaluation of these patients, as we have found serious unsuspected pathology with surprising frequency. Renal cell carcinoma, adrenal tumors, retroperitoneal lymphoma, hepatic metastases, iliac vein aneurysms, and vena caval atresia all have been identified. A full hematologic evaluation for an underlying thrombophilia is also performed.

Technique

There has been an evolution of catheter-directed thrombolytic techniques over the past several years. The preferred approach is through an ultrasound-guided popliteal vein puncture with antegrade passage of the infusion catheter. Through this approach physicians can incorporate adjunctive mechanical thrombectomy techniques.

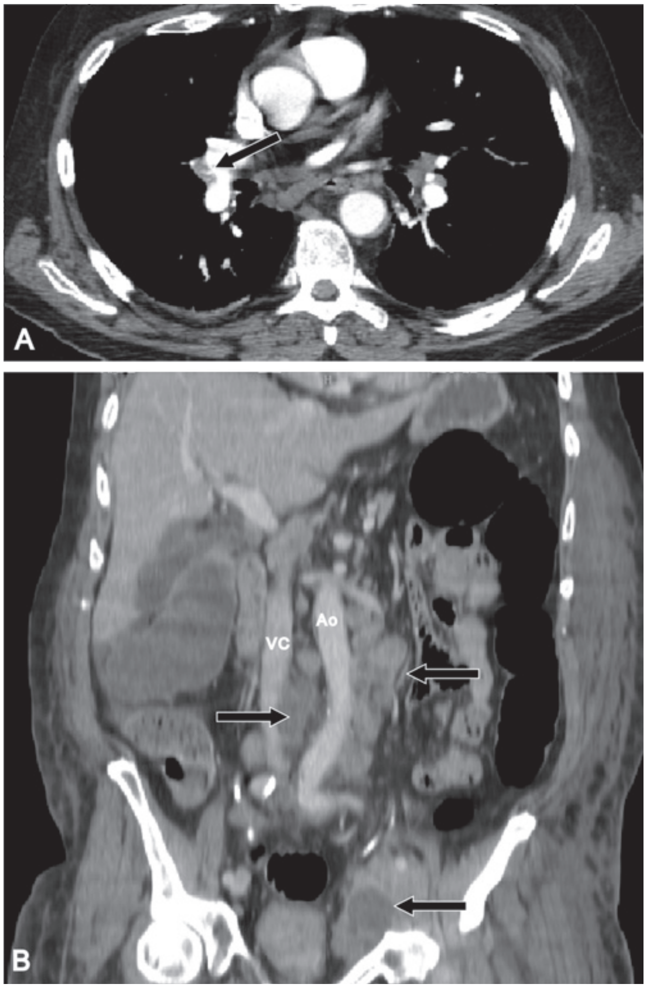

FIGURE 49.3 Initial CT scan of the chest, abdomen, and pelvis of a 65-year-old male with chronic low back pain who presented with left lower extremity phlegmasia cerulea dolens. The chest CT (**A**) shows an asymptomatic pulmonary embolus (arrow). The abdominal CT (**B**) shows extensive retroperitoneal and pelvic lymphadenopathy (arrows) compressing the distal vena cava and the left iliac system. All patients presenting with iliofemoral DVT by duplex ultrasound receive chest, abdominal, and pelvic CT scans as part of the initial workup.

If the popliteal vein is thrombosed, an additional catheter is placed through an ultrasound-guided tibial vein puncture. Using catheters that achieve long segments of thrombus infusion is advised.

There also has been an evolution in the dose and volume of plasminogen activator. Since the activation of fibrin-bound plasminogen is not dose dependent, exposure to the plasminogen activator is all that is required. The volume of the lytic solution has increased with a decrease in the concentration (dose) of plasminogen activator. It is now our preference to increase the volume of lytic infusion to 80 to 100 ml per hour. The larger volume is intended to saturate

the thrombus, exposing more fibrin-bound plasminogen to the plasminogen activator. Phlebograms are obtained at 12-hour intervals and are used to monitor the success of lysis and reposition catheters if necessary. Vena caval filters are not routinely used but are recommended for patients with free-floating thrombus in the vena cava. A retrievable filter can be used in the patient in whom only temporary protection is needed.

Following successful thrombolysis, the venous system is examined with completion phlebography. If a stenosis exists, which is frequently observed in the left common iliac vein where it is compressed by the right common iliac artery, the vein is dilated and stented if necessary. The addition of intravascular ultrasonography has improved the evaluation of iliac compression and the precision of stent deployment when these lesions are corrected. Residual areas of stenosis must be corrected for long-term success; otherwise, the patient faces a high risk of rethrombosis. If a stent is used, it should be sized appropriate to the normal diameter of the common iliac vein.

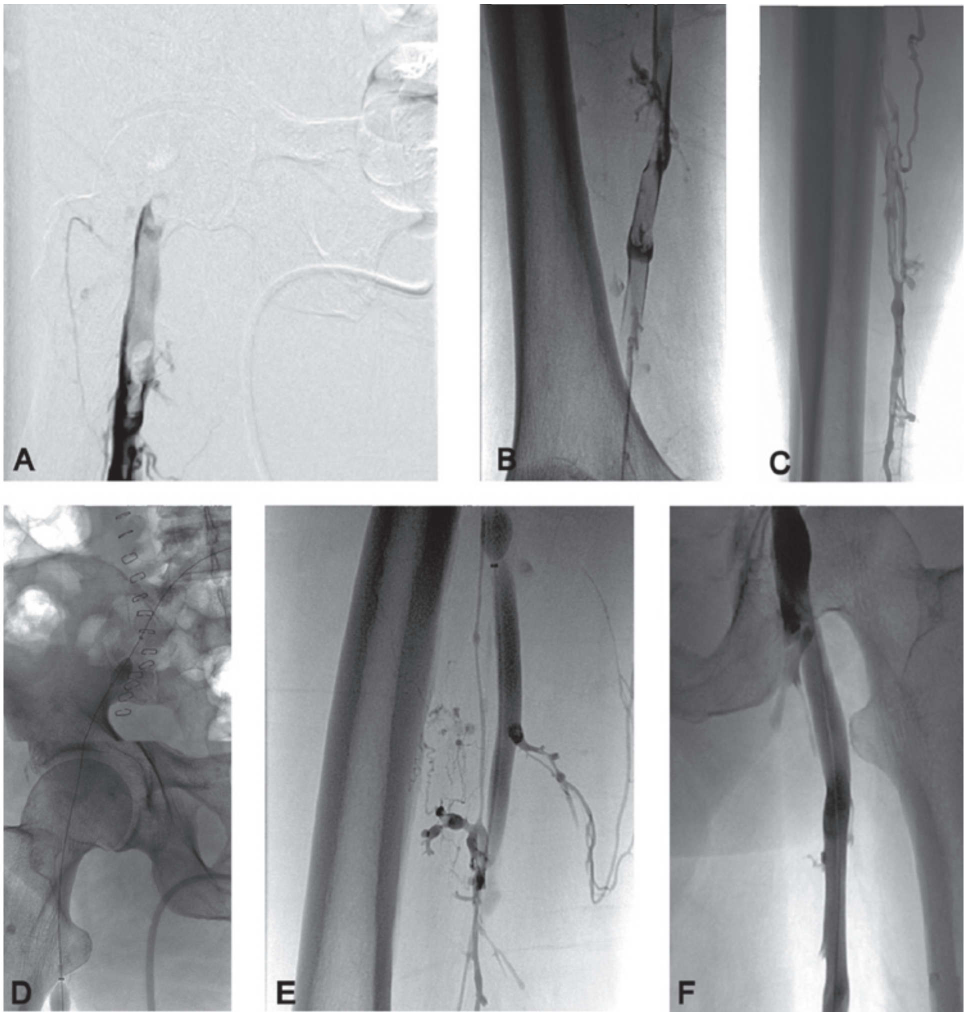

FIGURE 49.4 **A**, **B**, **C**. Phlebogram of a patient two days after exploratory laparotomy shows left iliofemoral, femoropopliteal, and posterior tibial DVT. The treatment goal was to lyse the extensive thrombus rapidly with minimal systemic exposure to the plasminogen activator. **D**. This was accomplished using segmental pharmacomechanical thrombolysis with the hybrid Trellis peripheral infusion system (Bacchus Vascular, Santa Clara, CA) and ultrasound accelerated thrombolysis of popliteal and tibial thrombus with the EKOS LysUS® System (EKOS Corp, Bothell, WA). The Trellis system achieves isolated thrombolysis between two occluding balloons by lytic infusion and mechanical drug dispersion with the intervening catheter rotating at 15,000 rpm. This mechanism of thrombolysis enables focused treatment of thrombus within the target vessel. **E**, **F**. Phlebogram 30 minutes after using the Trellis system shows resolution of the thrombus in the iliac and femoral veins.

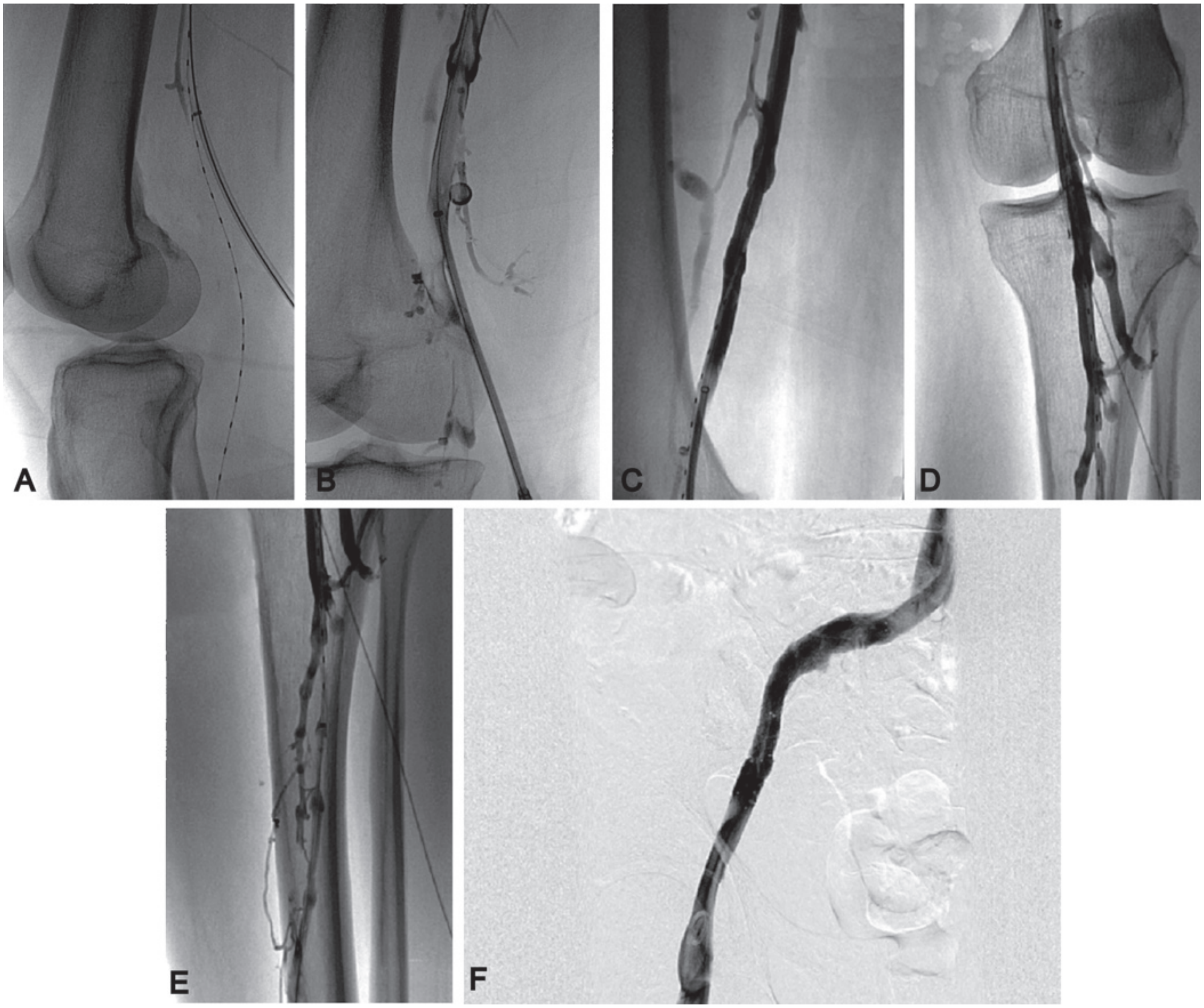

FIGURE 49.5 **A**. The EKOS LysUS® System (EKOS Corp, Bothell, WA) is an ultrasonic infusion system designed for controlled and selective infusion of thrombolytics into the thrombosed veins. Ultrasound waves accelerate thrombolysis, reducing treatment time. The catheter was advanced proximally from an ultrasound-guided posterior tibial vein puncture. **B**. Phlebogram showing popliteal vein thrombus. **C**. Post-ultrasound lysis, dissolution of thrombus in the distal femoral vein, **D**. popliteal vein, and **E**. posterior tibial vein. **F**. Angioplasty and stenting were performed on the left iliac vein, establishing normal venous drainage into the inferior vena cava.

ADJUNCTIVE TECHNIQUES TO CATHETER-DIRECTED THROMBOLYSIS

Percutaneous mechanical thrombectomy techniques are discussed in detail in Chapter 50. There appears to be a higher incidence of embolic complications with mechanical thrombectomy. In a prospective evaluation of pulse-spray pharmacomechanical thrombolysis of clotted hemodialysis grafts,[27] it was found that PE (documented by ventilation perfusion scan) occurred in 18% of patients treated with a plasminogen activator pulse-spray solution versus 64% of patients treated with a heparinized saline pulse-spray solution (P = .04). Since clotted hemodialysis grafts are in direct communication with the venous circulation, they can be considered similar to proximal veins with acute DVT. Observations would likely be magnified when treating larger venous thromboses.

In an experimental model, Greenberg and associates[28] evaluated mechanical, pharmacomechanical, and pharmacologic thrombolysis. Their findings are consistent with anecdotal clinical observations as well as the results reported by Kinney and associates.[27] Greenberg et al. demonstrated that

pulse-spray mechanical thrombectomy was associated with the largest number and greatest size of distal emboli. When urokinase was added to the solution, the embolic particles diminished in number and in size and increased the speed of lysis with reperfusion. Catheter-directed thrombolysis alone was associated with the slowest reperfusion but the fewest distal emboli. In general, mechanical thrombectomy alone most often is inadequate. Hemolytic complications of rheolytic mechanical thrombectomy are common and occasionally can result in anemia and renal dysfunction.

A new device recently released for segmental and controlled pharmacomechanical thrombolysis is the reengineered Trellis catheter (Bacchus Vascular, Santa Clara, CA), which is a hybrid catheter that isolates the thrombosed vein segment between two occluding balloons (see Figure 49.4). A lytic agent is infused into the thrombus between the occluding balloons. The intervening catheter shaft assumes a sign wave or spiral configuration and, when activated, spins at 15,000 rpm. After 10 to 15 minutes, the liquified thrombus and remaining fragments are aspirated. Phlebographic evaluation of the result is performed before moving on to treat additional thrombosed vein segments (see Figure 49.4). The advantages of such a device are its ability to incorporate mechanical and pharmacologic therapies, even in patients with a contraindication to thrombolytic therapy since the infusate is aspirated, and the rapidity with which treatment can be achieved. The rationales behind the design of this catheter are:

1. Rapidly resolve thrombus during a short course of treatment.
2. Limit or avoid exposure to thrombolytic therapy by aspirating liquified thrombus and infused lytic agent.
3. Prevent PE by proximal balloon occlusion.

A clinical trial designed to evaluate the success and complication rate of this technique is under way.

An interesting new adjunct to catheter-directed thrombolysis is the addition of the emission of ultrasound waves from the infusion catheter while delivering the plasminogen activator (see Figure 49.5). Several reports have emerged indicating that an infusion catheter with ultrasound transducers built into the infusion end of the catheter can be used to accelerate thrombolysis.[29–32] *In vitro* studies have demonstrated that ultrasound enhances the fibrinolytic activity of tissue plasminogen activator (t-PA).[33–35] The potential mechanism for augmented clot lysis has been extrapolated from *in vitro* studies showing that ultrasound produces clot fragmentation in the presence of t-PA, and consequently, more t-PA binds to fibrin-binding sites due to the larger available surface area.[36–38] The concept of a transducer-tipped catheter that delivers a fibrinolytic drug in combination with high frequency, low-intensity ultrasound has been well described. *In vivo* models[39] and clinical trials[40] are now under way to assess the potential value of ultrasound enhancement of thrombolysis for the management of acute DVT.

The patient with phlegmasia cerulea dolens, summarized in Figure 49.4, illustrates the advantage of using segmental, pharmacomechanical thrombolysis and ultrasound-enhanced catheter-directed thrombolysis to shorten treatment duration and limit exposure to the thrombolytic agent, maximizing the chance of a successful outcome.

Thrombolysis is effective and has become safer with the direct intrathrombus infusion and adjunctive mechanical techniques. As technology continues to improve, lytic infusion times will shorten, more patients will be offered a treatment strategy that includes thrombus removal, and many patients will be spared their otherwise certain post-thrombotic morbidity.

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CHAPTER

50

Percutaneous Mechanical Thrombectomy in the Treatment of Acute Deep Venous Thrombosis

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INTRODUCTION

Deep venous thrombosis (DVT) is associated with significant morbidity and mortality. Symptomatic DVT affects 250,000 to 300,000 people per year in the United States and is responsible for approximately 300,000 hospital admissions per year.[1–4] Nearly 50,000 deaths each year are attributable to pulmonary embolism (PE) from DVT.[3] The costs for treatment of DVT are estimated between $1.2 and $2.4 billion per year.[5]

Once the diagnosis of DVT is established, the goals of therapy are: 1) prevention of PE, 2) prevention of thrombus propagation, 3) preservation of valvular function, and 4) prevention of post-thrombotic syndrome (PTS). Traditionally, treatment involves unfractionated heparin (UH) or low molecular weight heparin (LMWH) as a bridge to oral anticoagulation. In addition to the prevention of PE and PTS, therapeutic anticoagulation aids in the prevention of clot propagation. Asbeutah et al. reported five-year follow-up of 51 patients with 54 DVTs for PTS. Twenty-six limbs were noted to have proximal involvement. When treated with anticoagulation alone, 34% had thrombus resolution at one month. Sixty-five percent of limbs went on to develop reflux and 54% progressed to chronic venous insufficiency within one year of diagnosis.[6]

Surgical thrombectomy is an open procedure whereby thrombus is manually extracted from a venotomy most commonly created in the femoral vein. Thrombus proximal to the inguinal ligament is removed using a balloon catheter and thrombus below is removed by compression of the limb with an esmarch wrap (Spectrum Laboratories, Rancho Dominguez, CA). Problems with this technique include denuding endothelium, damage to the valves, and incomplete thrombus removal. Although still advocated by some as the preferred method of treatment for DVT, the vast majority of patients continue to be treated with anticoagulation.

With the advent of thrombolytic drugs, some institutions have treated DVTs with intravenous administration.[7–9] Although thrombolysis theoretically satisfies all therapeutic goals, complete thrombus resolution occurs in only about 50% of patients with nonobstructive thrombus and 10% of those with obstructive thrombi.[10,11] Serious bleeding complications such as retroperitoneal hematoma and intracranial hemorrhage are markedly elevated in patients receiving systemic therapy when compared to patients treated with anticoagulation alone.[12–15]

Regional or catheter-directed thrombolysis (CDT) has been used with some success. Potential advantages include administration of the pharmacologic agent directly into the thrombus and less systemic side effects. AbuRahma et al. reported complete resolution of symptoms in 83% of patients undergoing CDT compared to 3% in the group receiving anticoagulation alone.[16] CDT also has proven advantageous in the prevention of recurrent DVT in a large majority of patients.[17] Unfortunately, bleeding complications continue to plague 4 to 6% of patients, and intracranial hemorrhage still occurs in a small minority of patients.[18,19] CDT usually requires one to three days of continuous therapy and represents a major disadvantage to prompt and safe treatment. Comerota et al. reported a 21% incidence of severe PTS in patients treated for DVT with heparin alone, compared to 5% in those treated with streptokinase.[20] CDT in the management of DVT also has been proven superior to anticoagulation alone when evaluating health-related quality of life.[21]

Percutaneous mechanical thrombectomy (PMT) refers to the technique whereby a catheter utilizing mechanical means

can be used independently or coupled with pharmacologic thrombolysis in the treatment of DVT. Preliminary data show that treatment with PMT may provide quicker thrombus resolution than CDT alone.[21,22] With an increasing emphasis on minimal invasiveness, recent years have witnessed an endovascular revolution that has ushered in many different types of PMT catheters. Herein we provide a comprehensive review of the PMT catheters and descriptions of more common treatment techniques.

TECHNIQUE

In order to successfully perform PMT, several general premises must be considered. These include whether to place a temporary vena cava filter, determining optimal site for venous access, and how to traverse the thrombosis. Although the technique unique to each PMT catheter is highly variable, these general principles apply to most clinical scenarios in treating DVT. Following thrombus removal, subsequent interventions such as balloon angioplasty and/or stenting can be performed if necessary.

Temporary IVC Filter Placement

The risk of fatal PE during thrombolytic therapy of iliac vein thrombus has been reported as high as 6%.[24] All PMT devices, including those that aspirate during treatment, generate small particles that can migrate to the pulmonary circulation. The placement of a retrievable IVC filter has become a valuable adjunct to PMT. There are many types of temporary IVC filters available with different time periods for retrieval (see Table 50.1). Additionally, each filter varies in the approach to deployment and retrieval. These important issues must be considered prior to PMT.

An *in vitro* model of early large volume DVT demonstrated that in placing an IVC filter prior to PMT, 99% of particles >500 μm were either macerated by the device or captured by the filter.[25] Trerotola et al. demonstrated a significant number of clinically significant segmental and subsegmental pulmonary emboli while evaluating the Arrow-Trerotola Percutaneous Thrombectomy Device (Arrow International, Reading, PA) in a canine model.[26] Further investigations determined that use of a temporary IVC filter reduced the number of pulmonary emboli as diagnosed by pulmonary angiography.[27]

In the majority of patients, placement of a retrievable IVC filter should be performed just prior to PMT. Generally, access to the deployment site should be void of thrombus and guidewire traversal should be observed with fluoroscopy for any deviation or difficulty that may indicate the presence of thrombus. A venogram should be obtained prior to deployment of the IVC filter to identify the renal veins and to further ensure the proposed deployment location is devoid of any thrombus. A low threshold to perform venography by selective catheterization should be considered if nonselective venography fails to show important venous tributaries.[28]

Depending upon the results of PMT, the filter can be removed immediately or remain in place one to three weeks during the healing process. The IVC filter should remain in place if contraindications to anticoagulation arise, development of recurrent DVT, or increases in DVT risk occur.

Venous Access

If possible, the same venous access for IVC filter placement should be used when selecting an access site to perform PMT. The ipsilateral common femoral vein is the optimal access site for thrombus confined to the iliocaval segments. In this clinical scenario, the IVC filter should be placed via the contralateral femoral vein. If the thrombosis is confined to a single lower extremity, possible access sites include either common femoral vein or the ipsilateral popliteal vein. The internal jugular vein can also be used to access DVT in the lower extremities.

TABLE 50.1 Retrievable IVC Filters

	Insertion sites			Retrieval sites		
Filter	Femoral	Jugular	Antecubital	Femoral	Jugular	Antecubital
ALN (ALN Implants Chirurgicaux, Ghisonaccia, France)	X	X	X		X	
Recovery (Bard Peripheral Vascular, Tempe, AZ)	X				X	
Günther Tulip (Cook Medical, Bloomington, IN)	X	X			X	
OptEase (Cordis Endovascular, Warren, NJ)	X	X	X	X	X	
SafeFlo (Rafael Medical, Caesarea, Israel)	X	X	X	X	X	X

Generally, access to LE DVT from the external iliac vein to the superficial femoral vein is from the contralateral common femoral vein. Selective catheterization comes over the iliac vein bifurcation and the involved contralateral venous segments are accessed in a retrograde direction. If the thrombus burden is high or there is anticipated difficulty in performing a retrograde cannulation, antegrade access through the ipsilateral popliteal vein is preferred.

The antegrade approach through the ipsilateral popliteal vein to treat iliofemoral DVT remains the most common alternative to the contralateral approach. With the patient in the prone position, duplex ultrasound is required for needle guidance. A micropuncture kit that uses a 22-gauge needle and a 0.014″ wire aids in providing a nontraumatic safer access. Advantages of antegrade access through the popliteal vein include ease of traversing valves and minimal need for selective catheterization.

Other more remote sites such as the jugular and subclavian veins have been used to gain access to DVT. More commonly these access sites may be required for direct access to the confluence of the common iliac veins. Occasionally, common iliac vein stenosis in combination with thrombosis can be negotiated only via a retrograde approach from the brachiocephalic veins. Treating iliofemoral DVT may require dual access with the use of a snare to pull the wire from one access site to another, thereby providing for more stable access to treat with PMT. In the case of upper extremity DVT treatment, venous access generally is obtained at the ipsilateral basilic vein. This also requires ultrasound guidance and use of a micropuncture kit.

Traversing the Thrombus

After defining the venous segment by venography as an entry point to the thrombus, stable access with a sheath or guiding catheter usually is required. A stiff hydrophilic guidewire (Boston Scientific; Natick, MA) allows optimal manipulation and guidance in gaining access into thrombus. As the wire is advanced, a catheter is advanced over the wire to maintain crossing and increase stability. Usually a straight catheter such as a 4 Fr. glidecath (Boston Scientific, Natick, MA) is used in combination with a stiff angled guidewire (Boston Scientific, Natick, MA). Alternatively, an angled catheter such as a Kumpe catheter (Cook; Bloomington, IN) can be used with a straight guidewire (Boston Scientific; Natick, MA). These combinations are particularly useful when traversing thrombus in a retrograde direction. Valve leaflets can be negotiated with slow directed movements under magnified fluoroscopy.

Another technique that can facilitate crossing thrombus is forming the guidewire into a long “J” configuration. This maneuver takes advantage of the stiff portion of the guidewire while preventing trauma to the vein wall because the floppy tip is in a “J” shape. When pushing antegrade through older thrombus, this technique may prove useful. Emphasis should be placed on not forcing wires, catheters, and PMT systems into position. Careful continuous fluoroscopic imaging is mandatory when moving wires and catheters and observing their tracking path is vital to avoiding injury. A manifold hand injection system with the ability to withdraw contrast and dilute with saline is helpful in facilitating quick, periodic views to assure correct catheter position.

DEVICES

PMT catheters can be categorized a variety of ways. One important distinction is whether the catheter has complete or incomplete wall contact. Advantages of complete wall contact include more thorough thrombus dissolution. Potential disadvantages include endothelial and valvular damage. PMT catheters also can be categorized by their method of thrombus dissolution. These mechanical methods include rheolytic aspiration, rotational thrombectomy, and ultrasonic fragmentation. Rheolytic devices remove thrombus based on the Venturi effect. This adaptation of the Bernoulli effect states that fluid moving at high speeds generates low pressure zones. These low pressure zones create a partial vacuum, termed the Venturi effect. In rheolytic thrombectomy devices, high speed saline jets are directed into the thrombus creating low pressure zones near the catheter where the fragments are aspirated through the device via the vacuum effect. Theoretic advantages of rheolytic aspiration include less valvular damage and decreased endothelial damage.

The rotational devices are designed to spin at varying speeds within the thrombus causing fragmentation. This mechanism also can result in increased endothelial damage. Ultrasonic fragmentation occurs through the delivery of high-frequency, low-energy ultrasound. The ultrasound waves cause the aggregated fibrin strands to dissociate resulting in both increased permeability of the thrombus and exposure of new plasminogen activator sites on the fibrin strands. Thrombolytic drugs are forced into the thrombus by the radial pressure generated by the ultrasound waves.

Finally, PMT catheters are designed to either aspirate fragmented thrombus or create a near liquefaction of thrombus that migrates into the venous circulation. Ultimately, the microemboli are propelled to the pulmonary circulation where endogenous lysis takes place. The aspiration catheters can increase blood loss associated with the procedure, and, therefore, the operator must be vigilant in monitoring the aspirated volume. Clinically significant sequelae of pulmonary emboli from the nonaspiration catheters have not been reported after treatment for DVT. Table 50.2 includes the commercially available devices subsequently discussed in this chapter.

TABLE 50.2 PMT Devices

Device	Method of thrombus removal	Wall contact	Aspiration catheter	FDA approved indication
AKónya Eliminator	Mechanical	Mechanical	No	Thrombosed AVF and dialysis grafts
Arrow-Trerotola	Mechanical	Complete	Yes	Thrombosed AVF and dialysis grafts
Angiojet				
XMI	Rheolytic	Incomplete	Yes	Coronary or vein graft lesions >2 mm
XVG	Rheolytic	Incomplete	Yes	Thrombosed infrainguinal arteries >3 mm
Xpeedior 120	Rheolytic	Incomplete	Yes	Thrombosed infrainguinal arteries >3 mm
AVX	Rheolytic	Incomplete	Yes	Thrombosed dialysis grafts
XMI-RX+	Rheolytic	Incomplete	Yes	Thrombosed infrainguinal arteries >2 mm
DVX	Rheolytic	Incomplete	Yes	Thrombosed infrainguinal arteries >3 mm
Castaneda Over-the-Wire Brush	Mechanical	Complete	No	Thrombosed dialysis grafts
Helix Clot Buster Thrombectomy Device (Amplatz Device)	Mechanical	Incomplete	No	Thrombosed AVF and dialysis grafts
Lysus Infusion System	Ultrasonic	Incomplete	No	Selective infusion of medication into peripheral vessels
Oasis Thrombectomy System	Rheolytic	Incomplete	Yes	Thrombosed dialysis grafts
ProLumen	Mechanical	Complete		Thrombosed dialysis grafts
Thrombex PMT	Mechanical	Incomplete		Thrombosed dialysis grafts
Trellis Infusion System	Mechanical	Incomplete	Yes	
X-Sizer Catheter System	Mechanical		Yes	Thrombosed dialysis grafts

AngioJet Thrombectomy System

Indications for use approved by the United States Food and Drug Administration (FDA) of the AngioJet thrombectomy system (ATS) (Possis Medical, Minneapolis, MN) include treatment of peripheral arterial occlusions, thrombosed hemodialysis grafts, and DVT. This dual lumen catheter (see Figure 50.1) operates on the Bernoulli-Venturi principles. Saline or a thrombolytic drug are infused by a drive unit to generate approximately 10,000 psi of pressure within the catheter. The infusate is ejected from the catheter in retrograde-directed, pulsatile jets. The jets generate low pressure zones that allow for thrombus maceration and aspiration. An exhaust port near the tip of the catheter allows for aspiration thereby avoiding the potential for localized endothelial damage from a more eccentrically placed vortex. Ninety-nine percent of the particulate matter generated by the ATS is 0 to 12 μm in diameter.[29] A separate pump drive unit is necessary for the catheter to function with dual lumen tubing that delivers the infusate and collects the effluent. The system functions in an isovolumetric manner with 60 cc/min being infused and aspirated simultaneously.[30]

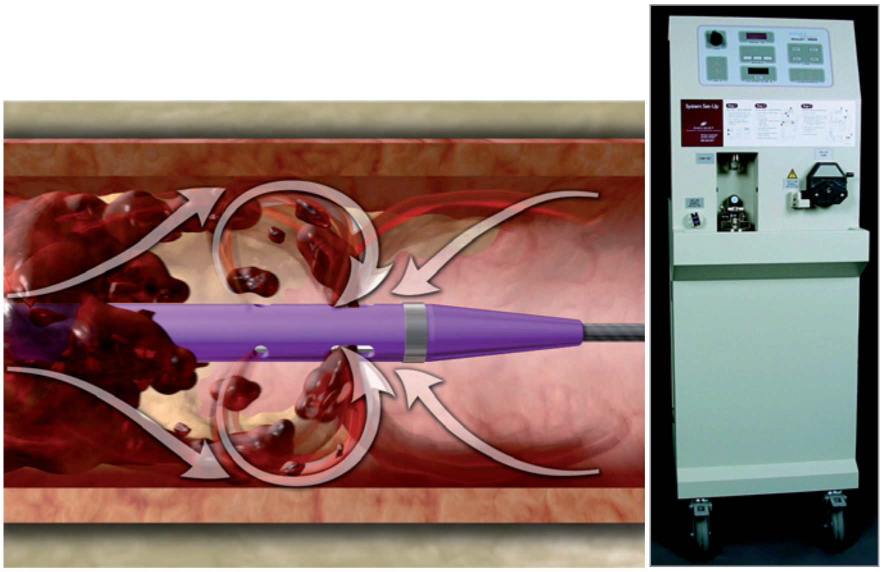
Multiple catheters have been designed for use in vessels of varying diameters and locations (see Table 50.3). Additionally, different types of tubing are available to allow for saline infusion or power pulsation. Power pulsation is designed to force standard pharmacologic thrombolytics into the thrombus. In contrast, traditional CDT uses *lacing*, whereby the drug seeps from the multiple side holes of an infusion catheter.

Sharafuddin et al. evaluated endothelial damage incurred after use of the ATS compared to the Fogarty balloon embolectomy in a canine model. The ATS-treated vessels had significantly more endothelial coverage than vessels treated with the Fogarty balloon.[31] Segments treated with the ATS showed no difference in endothelial coverage or valvular damage when histologically compared to untreated control segments.

TABLE 50.3 AngioJet Thrombectomy System Catheters

Catheter	Min. vessel diameter	Working length	Guidewire compatibility	Sheath compatibility
XMI-OTW	≥2 mm	135 cm	0.014″	4 Fr.
XMI-RX+	≥2 mm	135 cm	0.014″	4 Fr.
XVG	≥3 mm	140 cm	0.014″	5 Fr.
Xpeedior	≥3 mm	120 cm	0.035″	6 Fr
DVX	≥3 mm	90 cm	0.035″	6 Fr.

Thrombus extraction rates using the ATS range from 52 to 95%.[22] This wide range of variability appear to be related to the adjunctive use of pharmacologic thrombolysis.[32] The ATS has been used in the treatment of symptomatic lower extremity DVT with success. Bush et al. reported the use of the ATS in the treatment of 23 limbs in 20 patients. Technical success was achieved in 15 of the 23 treated limbs. The remaining limbs demonstrated varying degrees of thrombus removal. Seven of 12 patients being treated for iliofemoral DVT had prophylactic IVC filters placed. Marked clinical improvement within 24 hours of therapy was noted in 74% of patients. Only three minor bleeding complications were noted, and no one required a blood transfusion.[33]



A B

FIGURE 50.1 A. Demonstrates the Bernoulli-Venturi effect as used by the Angiojet thrombectomy system. B. The free-standing pump drive unit for the Angiojet thrombectomy system.

Kasirajan et al. reported similar results in 17 patients treated with the ATS. Thrombus extraction rates were lower with only 24% having >90% thrombus removal. Adjunctive thrombolytic therapy was used in nine of 13 that demonstrated less than 90% thrombus extraction. Eighty-two percent of patients had significant clinical improvement and no complications were reported.[34]

The ATS also has been successfully used in the management of Paget-Schroetter's syndrome, pulmonary embolism, and mesenteric venous thrombosis.[35–37]

Akonya Eliminator

The Eliminator catheter (IDev Technologies, Houston, TX) is a nonmotor-driven thrombectomy device approved by the FDA for thrombectomy of dialysis grafts. The device utilizes a 6 Fr. adjustable basket that can accommodate vessels from two to 10 mm in diameter. The catheter has directional control that allows easy navigation of tortuous vessels. The catheter has no drive unit, and through manipulation in an axial direction or manual rotation, the thrombus can be stripped from the vein wall.

Arrow-Trerotola Percutaneous Thrombectomy Device

The Arrow-Trerotola Percutaneous Thrombectomy Device (ATPTD) fragments thrombus utilizing a self-expanding 9-mm fragmentation cage. The device comes as either an over-the-wire configuration or the original design whereby the cage is constrained by a sheath. The latter device must be positioned across the thrombus before withdrawing the sheath and releasing the fragmentation cage. In both devices, the cage rotates at 3000 rpm and is pulled through the thrombus. The rotating cage strips and macerates thrombus from the vein wall creating a slurry that can be aspirated through the sheath. Two passes of the device usually provide optimal clot fragmentation.[38]

Damage to the veins after thrombectomy with the ATPTD was assessed in an experimental canine model. The device was passed five times in the antegrade direction through thrombosed lateral saphenous veins. The venous segments were assessed for endothelial loss, the presence of thrombus, and valvular damage. Compared to valves designated as controls in untreated thrombosed lateral saphenous veins, valves in the experimental group treated with ATPTD had significantly less inflammatory cell infiltrates.[39]

Technical success rates are reported between 92 and 100% when treating thrombosed dialysis grafts.[38,40,41] Procedure times are markedly shortened when compared to pulse spray thrombolysis.[38] Ninety-day patency rates range from 39 to 70%.[38,41] Preliminary work has begun to evaluate the ATPTD for treating DVT. Animal studies indicate promising local success rates, but segmental and subsegmental pulmonary emboli were demonstrated with concomitant increases in mean and systolic pulmonary arterial pressure. Increasing pCO_2 and acidosis were also observed.[42] The thrombus fragments produced by the device range in size from <1 mm to as high as 3 mm.[42] Truong et al. reported successful PMT using the ATPTD in a patient that presented with a subacute iliocaval thrombosis. A temporary Günther

basket filter was placed prior to intervention. At three months, magnetic resonance imaging (MRI) demonstrated no recurrent thrombosis in the treated vessels.[43]

HELIX Clot Buster

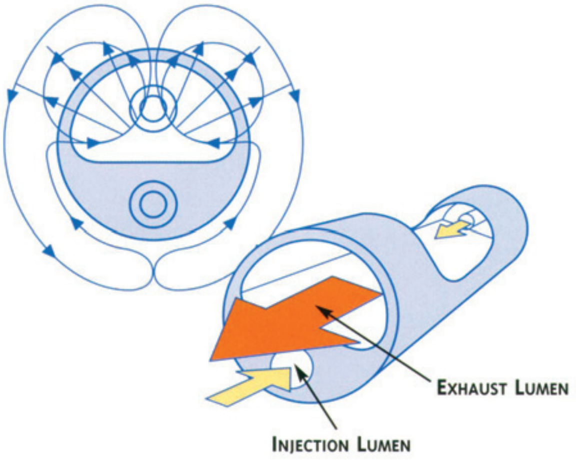
Previously marketed as the Amplatz Thrombectomy Device, the HELIX Clot Buster (ev3, Plymouth, MN) was the first device approved by the FDA for percutaneous treatment of thrombosed dialysis grafts. Basic components include an impeller mounted on a drive shaft that is powered by a compressed air turbine. Rotation of the impeller at 150,000 rpm creates a vortex at the distal tip of the catheter that draws in the thrombus and recirculates the particulate matter. Particles from this PMT catheter are less than 1000 microns.[44] Success rates of the HELIX for treatment of thrombosed dialysis grafts range from 79 to 93%.[45,46] The blunt tip design of the HELIX make it difficult to navigate tortuous vessels.

Successful treatment of venous thrombosis has been reported in multiple vascular segments using the HELIX. Uflacker reported treatment of nine acute and subacute venous thromboses in the IVC and iliac veins (n = 3), SVC and subclavian veins (n = 3), portal vein and transjugular intrahepatic portosystemic shunt (TIPS) (n = 2), and an IVC to pulmonary artery Fontan conduit (n = 1). Thromboses had been present from two days to four weeks. Three patients had failed prior CDT with urokinase. PMT was successful in all CDT failures, but each required an adjunctive measure to ensure long-term patency. One patient being treated for an iliocaval thrombosis developed intraprocedural shortness of breath attributed to pulmonary embolism despite placement of an IVC filter.[47] Similarly, Smith et al. reported using the HELIX in patients with DVT who had relative or absolute contraindications to pharmacologic thrombolysis. Treatment of DVT was performed in the superior mesenteric vein, bilateral femoral veins, and the SVC and brachiocephallic veins.[48] Additionally, the HELIX has been used to treat major and minor pulmonary emboli.[49]

Hydrolyser

This multilumen catheter (Cordis, Warren, NJ) is designed for over-the-wire use. It utilizes the Venturi effect to fragment thrombus (see Figure 50.2). Simultaneous infusion of thrombolytic drugs or saline is possible through an injection port. Aspiration takes place through a 6-mm elliptical exhaust port that is located 4 mm proximal to the distal tip of the catheter.

Disadvantages of the Hydrolyser (see Figure 50.3) can include possible fluid overload and hemolysis. Additionally, the guidewire may obstruct the exhaust port and decrease the amount of thrombus extracted. The eccentrically located exhaust port creates an imbalanced vortex. This may result



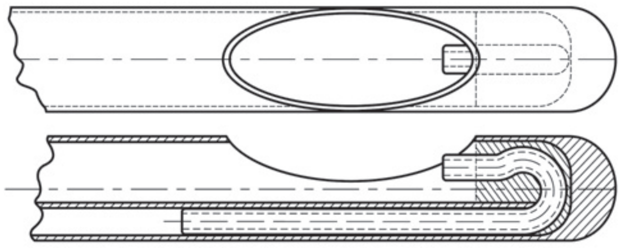


FIGURE 50.2 The Venturi effect as used in the Hydrolyser Catheter (Cordis Endovascular, Warren, NJ).

in tenting of the vessel toward the low pressure region and increase the endothelial damage.[22]

The Hydrolyser was compared to the ATS in an *in vitro* model to determine the degree of embolization.[50] The catheters were also compared with and without the guidewires in place, as previous data has indicated decreased effectiveness when the guidewire remained. The Hydrolyser demonstrated greater thrombus resolution and less distal embolization when compared to the ATS. Thrombus destruction was improved for both catheters when the guidewire remained in the catheter.[51]

Successful cases of PMT using the Hydrolyser for the treatment of acute DVT and pulmonary embolism have been reported.[52–54] Henry et al. reported 83% technical success in a variety of patients with arterial, bypass graft, and venous thrombosis.[53] Thrombus less than 10 days old provided the optimal therapeutic window when using the Hydrolyser, and segments treated took less than four minutes on average.[53] Poon et al. reported on three women that had IVC thromboses treated with the Hydrolyser. None of these patients could receive heparin or thrombolytics due to neurosurgical problems. All patients were successfully treated with the Hydrolyser and had complete resolution of their lower extremity edema. Each patient had an IVC filter placed, and one patient required a second treatment with the Hydrolyser.[54]

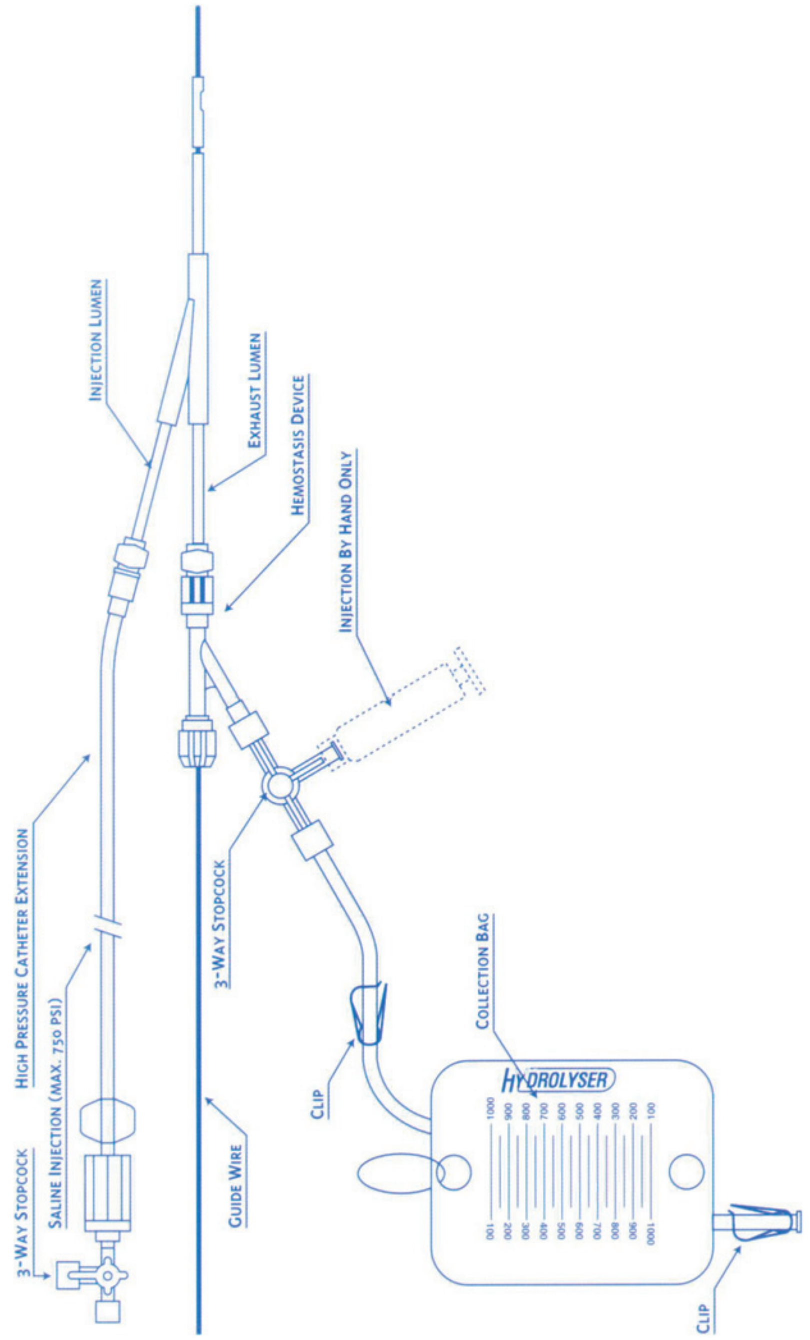


FIGURE 50.3 The Hydrolyser set-up.

Lysus Infusion Catheter System

The Lysus Infusion Catheter System (EKOS Corporation, Bothell, WA) uses high-frequency, low-powered ultrasound to lyse thrombus. After traversal of the thrombus with a guidewire, a multiholed drug delivery catheter is advanced over the guidewire. The guidewire is removed and the ultrasound core is placed within the catheter. The ultrasound core contains many ultrasound transducers along its length, and a separate control system regulates the ultrasound output and temperature. The core is actively cooled by a saline infusion that exits the distal tip of the catheter during treatment. Thrombolytic drugs are infused via the multiholed delivery catheter and the radial force generated by the ultrasound propels the drug away from the catheter and deeper into the more permeable thrombus.

Oasis

The Oasis catheter (Boston Scientific, Natick, MA), originally marketed as the Shredding Embolectomy Thrombectomy catheter, is a triple-lumen catheter placed over a guidewire that allows for the infusion of saline and simultaneous aspiration of thrombus. In contrast to the ATS system, which requires a separate drive unit, the Oasis can be powered by a standard power injector. The presence of the dedicated wire lumen also avoids a reduction in suction through the exhaust lumen that can be observed with the ATS device.

In a canine DVT model, the Oasis catheter has an 80% procedural success rate. All vessels exhibited endothelial denudation that occasionally extended into the internal elastic lamina while no injury extended to the media. Significant pulmonary embolization was not observed.[55]

Technical success in the treatment of thrombosed dialysis grafts approaches 90%, and clinical success, defined as the ability to access the grafts for dialysis, ranges from 76 to 81%.[56,57] Takahashi et al. reported a single case of successful use of the Oasis thrombectomy device to treat a symptomatic mesenteric venous thrombosis in the portal and superior mesenteric veins.[58]

ProLumen

Approved for use in hemodialysis access, the ProLumen (Datascope, Montvale, NJ) is a self-contained thrombectomy catheter that requires no additional equipment. The device contains a 0.035″ stainless steel S-wire with a radiopaque tip. With a 5.8-Fr outer diameter, the catheter has a handheld battery operated drive unit that rotates the sigmoid shaped S-wire at approximately 4000. The S-wire maintains contact with the graft wall to release adherent thrombus. No reports are published to date using the ProLumen for treatment of DVT.

Trellis-8 Thrombectomy System

The Trellis-8 Thrombectomy System (Bacchus Vascular, Santa Clara, CA) combines CDT and PMT by isolating the thrombosed venous segment between proximal and distal occlusion balloons. After a thrombolytic drug is infused into this closed system, a sinusoidal wire mixes the lytic agent into the thrombus together. The balloon occlusion limits systemic exposure to the lytic agent and prevents pulmonary emboli. The slurry created in the treated segment is then aspirated to remove lysed clot and the residual active drug.

The Trellis-8 Thrombectomy System (see Figure 50.4) has been successful in treating both upper and lower extremity venous thrombosis. Arko et al. reported use of the TTS to treat two patients with axillosubclavian vein thrombosis.[59] Ramaiah et al. used the TTS to treat an iliofemoral thrombosis. In both reports, use of the TTS resulted in shorter treatment times when compared to CDT alone, and decreased doses of the thrombolytic agent used. No bleeding complications were reported in any of the patients described. Neither patient described had a bleeding complication or pulmonary embolism reported.[59,60]

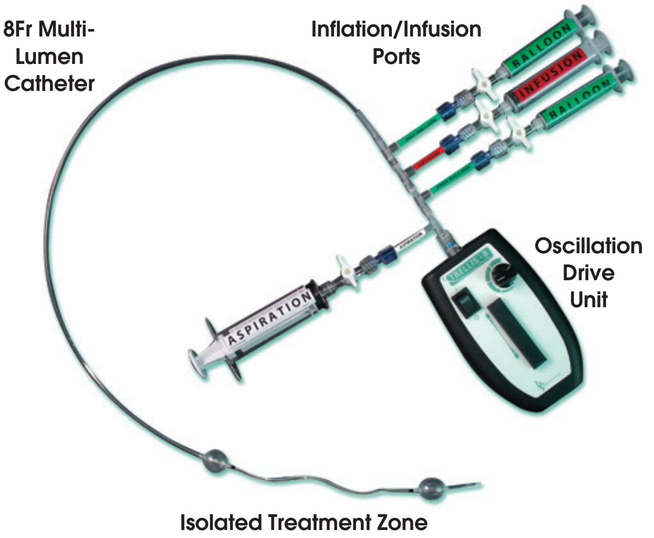


FIGURE 50.4 The Trellis-8 Thrombectomy System.

X-Sizer

The X-Sizer helical thrombectomy catheter (ev3, Plymouth, MN) is comprised of a rotating helical cutter that is housed in an outer sheath. The device is attached to a vacuum source for the aspiration of particulate matter created during the procedure. The device has been evaluated in the coronary arterial circulation, but to date treatment of hemodialysis grafts, the peripheral arterial tree, and the venous system has not been reported.

DISCUSSION

An increasing number of patients with acute DVT are undergoing treatment with PMT. Advantages of PMT include immediate improvement of symptoms, decreased treatment times and complications when compared to CDT alone, and a possible reduction in the incidence and severity of PTS. Although many PMT catheters are commercially available, only the Trellis-8 Thrombectomy System and the ATS lytic power pulse system are approved by the FDA for treatment of acute DVT.

Some PMT catheters, such as those just mentioned, are designed to allow for the concomitant infusion of thrombolytic agents in order to more thoroughly remove thrombus.

The combination of PMT and pharmacologic thrombolysis can drastically reduce the treatment times compared to CDT alone. Arko et al. reported complete thrombus removal in two patients using the Trellis-8 Thrombectomy System with Alteplase (Genentech, South San Fransisco, CA) for UE DVT. These two patients were treated at a single setting and received 5 mg of Alteplase over 10 minutes.[59]

When evaluating these devices in the treatment of thrombosed hemodialysis access, the ATS, ATPTD, and Oasis were found to have equivalent technical success rates when compared to pulse-spray thrombolysis.[28,56,61] The procedure times were significantly shorter in the groups that underwent PMT.[38,56] Complications such as bleeding requiring transfusion, pulmonary embolization, and arterial embolization were less in the PMT arm, but statistical significance was not reached due to the small number of patients.[38]

PMT most often allows patients to be treated in a single setting, thereby avoiding multiple trips to the angiography suite. Ramaiah et al. reported a single case of a patient that developed increased thrombus burden while on heparin. After failure following 36 hours of CDT with reteplase (Centocor, Horsham, PA), PMT using the Trellis-8 Thrombectomy System was successful with complete clot lysis in 45 minutes.[60] Similar results have been reported in the treatment of upper extremity DVT when using the Trellis-8 Thrombectomy System.[59]

Bleeding complications may be less when compared to CDT. In 17 patients treated with PMT for LE DVT, Kasirajan et al. observed no hemorrhagic or access site complications.[34] Bush et al. reported two patients that developed access site hematomas and one developed a retroperitoneal hematoma out of 20 patients treated for DVT with the ATS. None required surgical intervention or transfusion.[33]

The discovery of an underlying venous stenosis can occur after PMT. Thirty-eight to 95% of patients have been shown to have a lesion that is treated with percutaneous angioplasty or primary stenting. Importance should be placed on opening these stenoses so as to avoid outflow obstruction. Reducing outflow obstruction helps prevent recurrent DVT and further reduces the severity of PTS.

Many authors have described the use of various PMT catheters in the treatment of DVT. To date no prospective randomized *in vivo* trial has been performed comparing PMT to other various methods of DVT treatment. In an *in vitro* model, Müller-Hülsbeck et al. compared the ATS without a guidewire, with a 0.016″ guidewire, and with a 0.035″ guidewire to the Hydrolyser, Oasis, and Amplatz Thrombectomy. Interestingly, the ATS had significantly less thrombus removal using the 0.016″ guidewire compared to other configurations. No significant difference was found among the other catheters. The highest percentage of embolism was noted with the ATS.[50]

Delomez et al. reported use of the Amplatz Thrombectomy Device in 18 patients with symptomatic LE DVT. Successful recanalization was reported in 83% of patients. A permanent IVC filter was placed in one patient and a temporary filter placed in another. No pulmonary emboli were reported.[62] The time thrombus was present prior to treatment ranged from four to 240 days. The age of DVT that can still be optimally treated with PMT has not been determined. Generally two weeks represents a common window used by many practicioners.[47,62–64] Thrombus older than this begin to have a denser fibrin network and are more resistant to PMT. Moreover, older thrombi are associated with an increased incidence of distal embolization.[63]

PMT can also be used alone or in conjunction with thrombolytic therapy. In one study comparing multiple thrombectomy devices and lytic agents, Vendatham et al. reported improved results when coupling the two modalities compared to using either independently.[23] This retrospective review analyzed 20 patients who underwent 22 procedures. Due to the retrospective nature of the study, the methods of CDT and the timing and use of PMT could not be controlled. Vendatham reported an 82% procedural success when both modalities were combined. Major bleeding requiring transfusion occurred in three patients. Reduced doses and thrombolytic infusion times were observed in those undergoing adjunctive PMT. Based on his findings, he concluded that PMT has an important role in the endoluminal therapy for DVT.[23] Siablis et al. compared the ATS to CDT for the treatment of massive pulmonary embolism. He found significant decrease in the mean urokinase dose and duration of therapy in the ATS group.[36]

Many clinical scenarios exist in daily practice in which pharmacologic therapy with either thrombolytic agents or anticoagulation are contraindicated. Although an IVC filter can be placed for prophylaxis against PE, serious short- and long-term sequelae can still threaten the limb. Aside from the short-term decrease in quality of life from edema and pain, the long-term sequelae of PTS are devastating. Multiple reports illustrate resolution of edema, pain, and disability with the use of PMT alone.[33,34,48] Other advantages include minimizing bleeding complications and shorter hospital stays. The benefits of immediate improvement of leg edema following the use of PMT are underestimated. Although PMT is not indicated in some scenarios (e.g., patients with very poor prognosis and DVT), a majority of patients may prove to benefit. More prospective studies are needed to help determine who will benefit most. As technology continues to change rapidly, past studies can be difficult to interpret. Future research must also take into account quality of life measures in the short and long term.

Potential disadvantages of PMT are related to the individual catheter designs. Common to the catheters that utilize the Venturi effect is the potential for fluid overload resulting in congestive heart failure and pulmonary edema. The ATS, Hydrolyser, Oasis, and ATD are all designed to function in an isovolumetric manner. Müller-Hülsbeck et al.

evaluated all four PMT devices in an *in vitro* model, and found that none functioned isovolumetrically. The ratio of infused saline to aspirated fluid improved for the ATS when the guidewire was left in place. The Oasis was noted to have the greatest discrepancy between infused saline and aspirated fluid.[50]

Another potential disadvantage of all PMT catheters is hemolysis. Qian et al. found no significant differences regarding the hemolytic effect when comparing the Helix thrombectomy catheter and the ATD.[65] Gandini et al. evaluated plasma free hemoglobin (PFH) levels and hematocrit in eight patients treated for iliocaval thrombosis with the ATD, and found no significant abnormality in either parameter in any patient after treatement.[66] Uflacker reported a significant increase in PFH in 13 patients treated with the ATD. The PFH levels returned to normal within 24 hours.[47] In preclinical evaluations, treatement with the ATS resulted in a transient increase in PFH and a concomitant decrease in the hematocrit.[31] In 18 patients treated with the ATS for DVT, Delomez et al. reported no postoperative anemia. One patient developed a transient increase in haptoglobin without clinical sequelae.[62] However, Danetz et al. reported two patients with chronic renal insuffiency who developed pancreatitis after using the ATS.[67] The degree of hemolysis is directly proportional to the length of PMT. In patients with chronic renal insufficiency, minimizing the treatment time and careful attention to the hydration status may ameliorate the occurrence of post-treatment pancreatitis. Use of the ATPTD has not resulted in clinically significant elevation of the PFH after treatment of thrombosed hemodialysis grafts.[38]

Based on these observations, patients with renal and hepatic insuffiency should proceed with caution when considering PMT. The increased PFH can result in intranephronal cast formation resulting in acute renal failure. The increased PFH also increases heme catabolism, which enhances the formation of tetrapyrrol unconjugated bilirubin. The unconjugated bilirubin is metabolized and excreted by the liver. Those with abnormal liver function may not tolerate the increased PFH.[47] Although these considerations are paramount, no case of renal failure or fulminant hepatic failure has been reported after PMT.

CONCLUSION

PMT offers many benefits in short-term therapy for DVT. Faster thrombus removal, smaller doses of thrombolytic agents, and shorter treatment times translate into improved symptom relief, decreased complications, and more efficient patient care. Additionally, more rapid thrombus resolution potentially can preserve valvular function and decrease the incidence and severity of PTS. PMT should be considered as first line therapy for patients presenting with DVT. Advanced endovascular skills, as well as being well versed in possible complications of PMT, are required to provide safe and effective patient care.

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CHAPTER

51

Mechanical Thrombectomy and Thrombolysis for Acute Deep Venous Thrombosis

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INTRODUCTION

Deep venous thrombosis (DVT) is estimated to affect 20 to 30% of all major surgical patients, and, as a result of pulmonary embolism, is responsible for more than 60,000 deaths annually in the United States.[1,2] The current treatment strategy for acute DVT largely remains systemic anticoagulation to prevent worsening of acute symptoms, pulmonary embolism, and recurrent thromboembolic events. However, conservative therapy with anticoagulation alone is rarely efficient or sufficient in reducing clot burden to prevent post-thrombotic syndrome, particularly in iliofemoral systems. Endovascular interventions, on the other hand, provide the capability of rapidly reestablishing patency of the affected veins, potentially preventing post-thrombotic complications, and timely revealing an inciting venous defect in patients with acute DVT. This chapter emphasizes on the rationale, various methods, and results of thrombolysis for acute DVT.

EPIDEMIOLOGY

Deep venous thrombosis has been recognized as a major health problem in the western culture. Incidence of DVT has been estimated at over one per 1000 per year in the United States.[3] Similarly, the annual incidence in a British population studied was measured at 3.5 per 1000 per year.[4] In Sweden, the incidence has been estimated at 1.6 per 1000 per year.[5] Markel and colleagues followed a series of patients with DVT for a period of five years and discovered that most involved veins had recanalized by six months and over 80% were recanalized at one year. By three years, all veins had recanalized, but residual thrombus was present in 50%.[6] Additionally, they noted that symptomatic DVTs involved the proximal segments in 95% of patients.[7] The venous registry had similar findings of iliofemoral involvement in 71% and the femoro-popliteal segment in 25%.[8]

DVT is also a significant marker for mortality. The one-year mortality rate of DVT has been found to be 16 to 30% with most deaths occurring within the first month; this is at least three times as high as age-matched controls without DVT.[3,8]

CLINICAL PRESENTATION AND DIAGNOSIS

The classic presentations of DVT are swelling and tenderness, elevated temperature, and a positive Homans' sign (calf pain on dorsiflexion of the foot) (see Figure 51.1). In an extreme scenario, phlegmasia cerulea dolens, as evident by the painful blue appearance of the leg, can occur due to massive thrombosis involving the iliac veins and extending into the most distal venules in the leg. Phlegmasia cerulea dolens is a condition frequently associated with a hypercoagulable state or external obstruction, such as an underlying intraabdominal malignancy or May-Thurner syndrome.

Clinical diagnosis of DVT alone is unreliable due to only 50% of patients with evidence of DVT on venography having clinical symptoms. Venous duplex ultrasound, as the primary imaging technique, is extremely useful. Spectral Doppler can detect the presence of thrombus by determining normal or abnormal flow in the vessels. Normal Doppler will be unidirectional and spontaneous with respiratory phasicity. Flow should cease with Valsalva maneuver, and demonstrate augmentation by distal compression. The

FIGURE 51.1 A painful left lower extremity with severe swelling and erythema due to acute deep venous thrombosis.

Doppler will appear abnormal when there is substantial occlusion of the vein. Flow augmentation and Valsalva will be diminished or absent. The most reliable method for detecting thrombus is compression. Compressions are done in gray scale in a transverse plane. The thrombus can only be ruled out when vessel walls completely collapse. Partial thrombosis may be present if the entire vein does not collapse.

COMPLICATIONS AND POST-THROMBOTIC SYNDROME

The potential complications of acute DVT include venous gangrene, pulmonary embolism, recurrent thromboembolic events, and the development of chronic venous insufficiency or post-thrombotic syndrome. Anticoagulation therapy, the current standard of care for acute DVT, may inhibit further clot propagation and prevent pulmonary embolism. However, it does not in itself prevent chronic post-thrombotic complications. The consequences of chronic venous insufficiency and post-thrombotic syndrome are a major medical problem and often results in a significant lifestyle compromise for the patient. DVT can render the venous valves incompetent, resulting in a spectrum of clinical presentations ranging from telengectasias and varicose veins through chronic lower extremity pain and edema to venous skin changes with lipodermatosclerosis and ulceration. The incidence of post-thrombotic syndrome following proximal venous thrombosis has been measured at 16 to 82%.[3,9] The incidence of ulceration has been estimated at 3 to 8% following DVT. Following extensive lower extremity deep venous thrombosis, the post-thrombotic syndrome may manifest immediately or take several months or years to full patient debilitation.[10]

Controversies still exist over the pathophysiology of post thrombotic syndrome. Some authors believe that the primary mechanism is reflux, whereas others think that it is the combination of reflux and obstruction that leads to the most severe symptoms. Johnson studied the natural history of DVT by utilizing duplex ultrasound and demonstrated that the combination of reflux and obstruction were three and a half times more likely in the legs with evidence of post-thrombotic syndrome than in those legs that appeared normal.[11] Their findings are also supported by Mohr and his colleagues, who demonstrated a progressive increase in post-thrombotic syndrome over 20 years.[9] The highest risk group in their study were those patients under 40 with proximal DVT, who were three times more likely to develop post-thrombotic symptoms than other groups.

Longer duration of venous occlusion has been shown to increase the likelihood of secondary reflux, and thus post-thrombotic syndrome.[6,12] Additionally, the extent of the original DVT, particularly multilevel disease and recurrent thrombosis, has been associated with an increased incidence of post-thrombotic syndrome.[13] Techniques aimed at valve preservation and restoration of venous patency theoretically should decrease venous hypertension, thus reducing the incidence and degree of post-thrombotic symptoms. Improvements in venous hemodynamics also should lead to overall improvement in clinical symptoms. In fact, studies have shown that earlier clearance of the clot burden led to preserved valvular function and less symptoms.[8,14]

SURGICAL THROMBECTOMY

Surgical thrombectomy with distal arteriovenous fistula creation for acute DVT is mainly of historical interest because of its associated operative morbidity primarily related to blood loss and poor clinical outcomes. However, surgical thrombectomy may still be used in the clinical setting of venous gangrene with impending limb loss. The best reported results are from a 1999 study by Juhan et al.[15] These authors demonstrated an improvement in long-term results following surgical venous thrombectomy for acute iliofemoral DVT in their personal series.[15] In a review of 77 patients, principally young trauma victims, valvular competency was preserved at five years in 80%, and 90% of limbs had either mild symptoms of chronic venous insufficiency or no symptoms at all. Additionally, Meissner and colleagues reported their results of venous thrombectomy with arteriovenous fistula in 30 patients.[16] In all but three patients, patency of the iliofemoral segment was maintained 12 months after clot extraction. However, other series have demonstrated only average results for this all but abandoned technique.

THROMBOLYSIS

In light of the morbidity of post-thrombotic syndrome, more aggressive treatment regimens for acute DVTs have been proposed. The early reports of surgical thrombectomy and its impact on post-thrombotic syndrome encouraged development of nonsurgical methods to remove clots and achieve the same goals with minimally invasive means. Thrombolysis of DVTs offers potential rapid clearance of thrombus from the obstructed segments and reduction of subsequent obstruction and reflux. A review done by Comerota of 13 studies comparing thrombolysis versus anticoagulation confirmed the efficacy of thrombolysis.[14] Their review also confirmed that successful thrombolysis was associated with a lower incidence of post-thrombotic syndrome and improved venous function during long-term follow-up.

There are various means of achieving thrombolysis of occluded venous segments. The basic options are chemical thrombolysis given either systemically or catheter-directed into the thrombus, percutaneous mechanical thrombectomy (PMT), or the combination of the two, termed pharmacomechanical thrombectomy.

Systemic Thrombolysis

Early reports documented success in treating phlegmasia with streptokinase, with enthusiastic reports of excellent results “beyond expectation.” Since then, several investigators have found benefits of systemic thrombolysis.[8,14] Comerota and Aldridge reviewed data from 13 studies comparing anticoagulant therapy with thrombolytic therapy for DVT in 591 patients.[14] They found that complete lysis was observed in 45% of patients who received lytic therapy vesus 4% of patients treated with heparin alone. In addition, patients with successful lysis had a lower incidence of post-thrombotic syndrome and improved long-term venous function during long-term follow-up.

Not all reports of systemic thrombolysis had favorable results. In a report of 250 patients with received systemic or local therapy with rt-PA, streptokinase, or urokinase, Schweizer found significantly greater patency and reduced incidence of post thrombotic syndrome in the group with lysis.[17] However, when taking into account a 5% major bleeding complication rate and an apparent increase in pulmonary embolism, they recommended selective use of systemic thrombolysis for limb-threatening situations only. Other studies also echo this observation.[18]

Catheter-Directed Thrombolysis

The delivery of a pharmacologic lytic agent directly into an existing venous thrombosis has overtaken systemic thrombolysis due in part to more complete clot lysis combined with a lower rate of bleeding complications. By using one of the many commercially available multiple sidehole infusion catheters, higher drug concentrations are delivered directly to the location of the thrombus. An analysis of multiple studies by Comerota and Aldridge demonstrated increased success in treating patients with iliofemoral DVT by utilizing catheter-directed thrombolysis.

Catheter-directed thrombolysis has been advocated because of its theoretical advantage of complete and rapid clot dissolution. Multiple studies have documented the efficacy of several lytic agents in the treatment of acute DVT, with total infusion times needed for thrombus removal ranging from hours to days.[19–23] An association between time to lysis and the development of venous reflux was evaluated in patients using serial duplex scans following a DVT episode.[24] With the exception of the posterior tibial vein, early lysis and rapid venous recanalization appears to protect valve integrity in the lower extremity. Although catheter-directed thrombolysis results in early thrombus clearance and thus, potential lower incidence of post-thrombotic syndrome by preservation of valvular function,[19] the complicated profile of the lytic agent and the infusion times may limit its widespread use.

Technique for Catheter-Directed Thrombolysis

All procedures are performed in a fully equipped operating room with endovascular capabilities. Local anesthesia with light sedation is administered in most patients, whereas general anesthesia is used for patients not tolerating local anesthesia with sedation. For acute lower extremity DVT, the popliteal vein is cannulated using ultrasound-guided venous puncture techniques with the patient in the prone position (see Figure 51.2). Brachial vein is commonly accessed for acute upper extremity DVT. Following puncture of the vessel with a 21-gauge needle, a 0.014″ guidewire is inserted and subsequently exchanged for a 0.035″ guidewire. A 6 French guiding sheath next is advanced into the vessel. Hand injection of 10–15 cc contrast is performed to confirm the diagnosis as well as define the anatomy and extent of the thrombus (see Figure 51.3). A 0.035″ angled guidewire (Boston Scientific, MA) frequently is used to navigate through the occluded vein with relative ease in the setting of acute DVT. Next, the lysis catheter (Mewissen, Boston Scientific) with appropriate infusion length is advanced over the guidewire.

We typically start infusion by injecting 1- to 2-mg tissue plasminogen activator (tPA) through the catheter. Note that the Mewissen catheter must have a guidewire inserted to block the end hole and force the lytic agent through the side-holes. The tPA then is infused at the rate of 0.5 to

FIGURE 51.2 Cannulation of the popliteal vein using ultrasound-guided venous puncture techniques with the patient in the prone position.

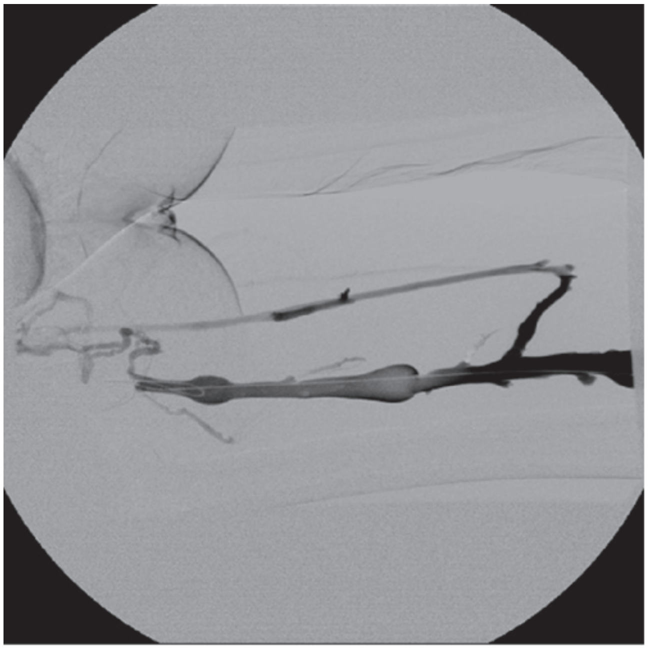

FIGURE 51.3 Ascending venogram being performed following cannulation of the popliteal vein to confirm the diagnosis as well as define the anatomy and extent of the thrombus.

1 mg/hour through the catheter, and heparin at 500 units/hour is infused concurrently through side port of sheath.

The patient subsequently is returned to the endovascular suite after 12 to 24 hours thrombolysis. A 0.035″ guidewire is inserted and the infusion catheter is removed. A repeat venogram is next performed by using hand injection of the contrast. A new catheter may be placed and repositioned to continue infusion if necessary. Once maximal thrombus removal has been achieved, angioplasty often is performed to macerate the residual thrombus (see Figure 51.4). Additional stents may be used for stenotic areas. The most common location of extrinsic venous compression is at the junction of the left common iliac vein with the inferior vena cava. However, stenting of all areas with residual stenosis is performed, even if it necessitates crossing the hip joint. Wallstents are our stent of choice for venous angioplasty,

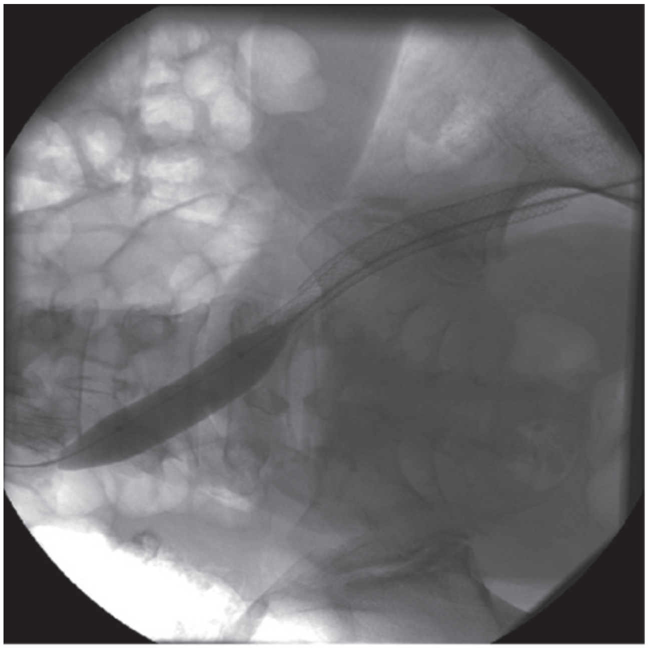

FIGURE 51.4 Angioplasty being performed to macerate the residual thrombus and achieve a patent venous lumen.

because of the large diameters and lengths. Failure to adequately resolve stenosis will result in rethrombosis.

PERCUTANEOUS MECHANICAL THROMBECTOMY (PMT)

Although thrombolysis, both systemic and catheter-directed, is effective in relieving clot burden early and potentially decreasing post-thrombotic complication, the bleeding risks due to lytic agents have limited its usage. Therefore, PMT has emerged as an advantageous option for the treatment of acute DVT. There are several commercially available thrombectomy catheters (see Table 51.1). However, a full discussion of each of the catheters is beyond the scope of this article. The catheters fall into one of two categories for clot extraction mechanism: microfragmentation or thrombo-aspiration (so-called Venturi effect). Several PMT catheters may be used in combination with adjunctive thrombolytic agents for more complete and rapid thrombus removal with lower lytic infusion doses and durations. Reducing the dosage and/or time for complete thrombolysis should translate into cost savings and lower bleeding complications. Furthermore, inciting lesions leading to thrombosis may be unmasked with PMT with or without adjunctive lysis. Venous stenoses could be treated following PMT and/or thrombolysis in the same operative setting. Our experience is with the AngioJet® thrombectomy system (Possis Medical Inc., Minneapolis, MN), which will be described in this chapter.

TABLE 51.1 Commercially Available and Investigational Thrombectomy Devices

Catheter name	Mechanism of clot extraction	Clot suctioning capability
AngioJet (Possis, Inc.)	Venturi	Yes
Hydrolyser (Cordis, Inc.)	Venturi	Yes
Oasis (Boston Scientific/Meditech)	Venturi	Yes
Amplatz (Microvena)	Microfragmentation	No
Helix (EV3)	Microfragmentation	No
Treretola (Arrow International)	Microfragmentation	No
Casteñeda and Cragg Brush (Micro Therapeutics)	Microfragmentation	No
Trellis infusion catheter (Bacchus Vascular)	Microfragmentation	Yes

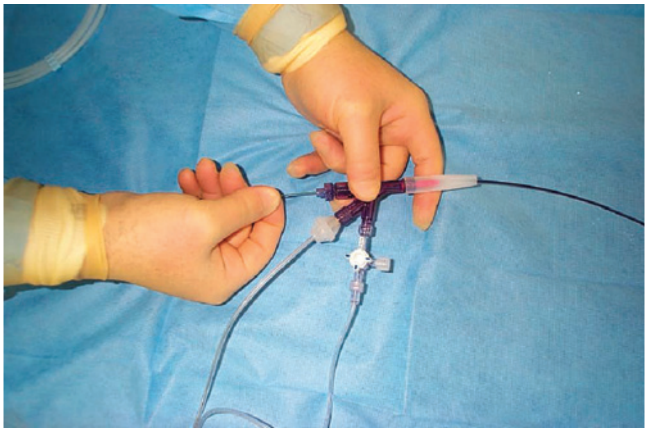

FIGURE 51.5 A three-way stopcock is placed on the AngioJet Rheolytic catheter outflow lumen between the catheter and the aspiration tubing. The stopcock is in the off position converting the catheter into a lytic infusion system.

Several authors have evaluated multiple PMT catheters in the treatment of DVT. However, to date, there is no prospective, randomized trial data available. In one review, Vedantham et al. used percutaneous mechanical thrombectomy (several devices tested including Amplatz Thrombectomy Device, Microvena, White Bear Lake, MN; AngioJet; Trerotola Percutaneous Thrombectomy Device, Arrow International, Reading, PA; Oasis, Boston Scientific/Meditech, Natick, MA) with catheter-directed thrombolysis for the treatment of lower extremity DVT.[25] Procedural success was achieved in 82% of the patients with underlying culprit stenoses uncovered and stented in 15 patients (18 limbs). These authors reported substantial thrombus removal with the two techniques combined compared to either alone. Another group, using only the Amplatz Thrombectomy Device, reported successful recanalization of the thrombosed segment in 83% of patients with proximal DVT.[26] At 29.6 months follow-up, 10 patients had no or minimal symptoms relating to the episode and only one patient had developed post-thrombotic sequelae.

Angiojet® Rheolytic Thrombectomy System Description

The AngioJet® rheolytic thrombectomy system consists of three components: a single-use catheter, a single-use pump set, and a pump drive unit. The 6 Fr Xpeedior catheter has a working length of 60, 100, or 120 cm, is introduced via a percutaneous approach (6 Fr sheath) and operates over a 0.035″ guidewire. The dual lumen catheter design consists of one lumen supplying pressurized saline to the distal catheter tip, and a second lumen incorporating the first lumen, guidewire, and thrombus particulate debris. The drive unit/pump generates high pressure (~10,000 psi) pulsatile saline flow that exits the catheter tip through multiple retrograde-directed jets. These high-velocity jets create a localized low-pressure zone (Bernoulli effect) for thrombus aspiration and maceration. The jets also provide the driving force for evacuation of thrombus particulate debris through the catheter. The Xpeedior catheter design also has a means for radially directed low-velocity fluid recirculation to assist with dislodgment from the vessel wall and direction to the catheter tip for evacuation. The AngioJet® system works in an isovolumetric manner: the saline infusion flow rate (60 cc/min) is in balance with the evacuation rate of thrombus particulate debris.

The infusion solution of saline may be replaced with saline mixed with a thrombolytic agent (1000 L saline combined with 250,000 u urokinase). A three-way stopcock is placed on the catheter outflow lumen between the catheter and the aspiration tubing. The stopcock can be positioned in the off setting, thus converting the thrombectomy catheter into a high pressure infusion—labeled "power pulse spray" by interventionalists who use this technique (see Figure 51.5). After lacing the thrombus with the pharmological agent and waiting an appropriate period of time (average 20 minutes), the stopcock is resumed in the open position and aspiration performed (see Figure 51.6). If concern exists for pulmonary embolism during this procedure, a dual-purpose removable/permanent vena caval filter may be placed at the beginning prior to PMT.

Technique of PMT for the Treatment of DVT

The AngioJet® rheolytic thrombectomy system is approved by the FDA for clot removal, particularly coronary arteries and hemodialysis grafts. The techniques described herein represent preferences of the authors based on experience, not recommendations from a manufacturer. Subsequent interventions such as endovascular stenting depend upon the judgment of the treating physician.

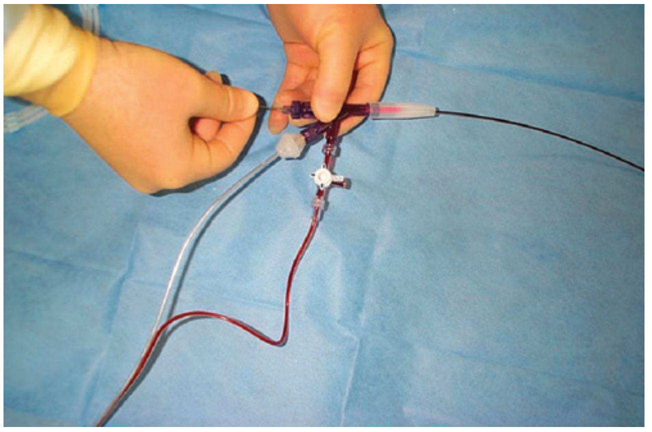

FIGURE 51.6 The stopcock in the on position, resuming thrombus aspiration.

All procedures are performed in a fully equipped operating room with endovascular capabilities. The patients are placed in a prone position and the ipsilateral popliteal vein is cannulated using ultrasound guidance for lower extremity DVT. After the initial ascending venogram is performed, the AngioJet® catheter is advanced over a guidewire and through the thrombosed vein segment. It is at this point that adjunctive thrombolytic agent is added to the infusion solution. A stopcock is added to the catheter outflow lumen as previously described and placed in the off position to close the outflow. One slow pass, withdrawing the catheter, is made to lace the thrombus with the lytic drug. After waiting 10 to 20 minutes to allow for more complete lysis, the outflow lumen is opened and mechanical thrombectomy performed to remove any residual clot burden. This sequence may be repeated in the event that significant residual thrombus remains on subsequent venograms.

Upper extremity DVT may be treated using the same technique. With this method, venous patency should be able to be restored in the operating room or interventional suite, obviating the need for intensive care unit stays or multiple trips for repeat venography. Furthermore, in our experience, lower total doses of thrombolytic agent are used than with catheter-directed thrombolysis. This translates into lower overall cost and a reduction in potential hemorrhagic complications. Adjunctive endovascular techniques, such as balloon angioplasty with or without stent placement, may be performed in the same setting of pharmaco-mechanical thrombectomy.

CONCLUSION

Despite compelling clinical results of thrombolysis and thrombectomy for the treatment of acute DVT, well-designed clinical trials are generally lacking. The optimal treatment for acute DVT is not completely clear. Although the occlusive effects of DVT can quickly and effectively be treated with thrombolytic therapy, bleeding complications are significantly increased. Whether lytic therapy lessens the destructive effects of DVT on valve function and leads to significantly improved clinical outcome is the crucial question yet to be elucidated. With the increasing literature supports of early clot resolution associated with the reduction of post-thrombotic syndrome, thrombolysis, mechanical thrombectomy, and aggressive treatment of underlying lesions for acute DVT should be considered for patients with a reasonable life expectancy.

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CHAPTER

52

Diagnosis and Management of Primary Axillo-Subclavian Venous Thrombosis

NIREN ANGLE

BACKGROUND AND HISTORY

Venous thrombosis resulting from compression of the axillo-subclavian vein at the thoracic outlet is a condition that, in contrast to most vascular disorders, afflicts young, otherwise healthy, and frequently quite physically active individuals. It is the venous manifestation of thoracic outlet compression, otherwise known by its eponym—Paget-Schroetter syndrome. Sometime around the 1950s, the term thoracic outlet syndrome (TOS) crept into the parlance of the medical and surgical literature, and was first used to describe both the arterial and neurogenic conditions, recognizing the not-infrequent overlap between the vascular and the neurologic manifestations of compression at the thoracic outlet. As Machleder has written, ". . . neurovascular compression at the thoracic outlet is perhaps best developed in the context of the historical evolution of etiologic concepts, and the unique anatomic characteristics that underlie the varied clinical manifestations."

The first two cases of spontaneous or effort-related axillo-subclavian vein thrombosis were published independently over 100 years ago by Paget in England[2] and Von Schroetter in Germany.[3] In 1949, ESR Hughes analyzed 320 cases of spontaneous upper extremity venous thrombosis in the medical literature and in recognition of the fact that this represented a unique disorder, named it the Paget-Schroetter syndrome.[4] At that time, surgical thrombectomy was the mainstay of therapy, with the goal being to restore venous patency, and was attended by high early rethrombosis rates. Until the 1980s, this remained the mainstay of therapy, at which time the availability of catheter-directed thrombolysis introduced a significant improvement in the treatment of this condition.

A significant amount of natural history data of this condition is available, which attests to the fact that untreated patients with Paget-Schroetter syndrome develop varying degrees of disability as a result of the chronic venous hypertension accompanied many times with recurrent episodes of venous thrombosis. Tilney et al. reported a 74% incidence of related disability,[5] whereas Linblad from Sweden reported it in the range of 25%.[6] In addition, there is a finite incidence of pulmonary thromboembolism as well.[7] Upper extremity venous thrombosis accounts for approximately 2% of deep venous thrombosis. In sum, Paget-Schroetter syndrome represents a condition that afflicts a young, active, and productive segment of the population, and if not aggressively treated, will result in significant disability that affects the function and productivity of this group of people.

THE ANATOMY OF THE THORACIC OUTLET

The superior opening of the bony thorax is now considered to be the thoracic outlet, sometimes termed the superior thoracic aperture. The anatomic features of the thoracic outlet are descriptive in their own right in terms of explaining the varied clinical manifestations that encompass the thoracic outlet syndromes, namely the arterial, venous, and neurogenic TOS subtypes.

In a review in 1986, the neurologist WS Fields wrote: "All shoulder girdle compression syndromes have one common feature, namely, compression of the brachial plexus, the subclavian artery, and subclavian vein, usually between the first rib and the clavicle. With elevation of the upper limb, there is a scissorlike approximation of the

clavicle superiorly and the first rib inferiorly. Grouping the various conditions under the single heading of thoracic outlet syndrome has resulted in more correct diagnosis and improved therapy."[8]

The anatomic feature underlying compression in the thoracic outlet is the presence of four spaces through which the neurovascular structures must traverse in their path from the neck to the axilla. These four spaces are the superior thoracic aperture, the interscalene triangle, the costoclavicular passage, and the subcoracoid space.[9] Of these, the interscalene triangle is a space bordered by the anterior scalene muscle anteriorly, the middle scalene muscle posteriorly, and the first rib inferiorly. The subclavian vein can be also compressed by first rib anomalies or by abnormal muscular insertions.[1,10] The costoclavicular space is most commonly the area where the subclavian vein is compressed in Paget-Schroetter syndrome; this is a space made up of the subclavius muscle anteriorly, the clavicle anteriorly, the first rib posteriorly, and the scapula and subscapularis muscle posterolaterally.

The inciting cause of Paget-Schroetter syndrome now is recognized to be a mechanical abnormality at the costoclavicular portion of the axillo-subclavian vein, which then results in superimposed thrombosis. The thrombosis always occurs in the area of chronic compression and resultant narrowing at the thoracic outlet. The vein is compressed between a hypertrophied anterior scalene muscle or subclavius tendon and the first rib. One may also occasionally see a large exostosis at the costoclavicular junction.

PRESENTATION

The male-to-female ratio is approximately 2 : 1 and the mean age distribution is in the third decade. Patients typically will provide a recent history of strenuous or repetitive upper arm activity prior to the onset of symptoms. The typical patient is one who is either a competitive athlete or one whose profession requires repetitive upper arm exertion. If one peruses the literature, it is clear that this is primarily a condition of the young/middle aged and/or active person, and as such, the condition is quite disabling. It afflicts men as well as women and the typical patient may be a student that swims, plays tennis competitively, lifts weights, or alternatively, a fireman, professional athlete, or a worker that performs heavy and repetitive lifting.

In a group of 50 consecutive patients at UCLA treated for Paget-Schroetter syndrome, Machleder described 31 men with a mean age of 24 (range 14–50 years) and 19 women with a mean age of 38 (range 23–51 years).[11] All but one of the men had been engaged in vigorous physical activity at the time of the onset of symptoms, and 10 of these were student athletes. Eleven women were engaged in sedentary occupations and eight were involved in activities involving upper extremity exertion.

The patient will typically suddenly notice severe and uniform swelling of the upper extremity. Usually, there is a slight rubor or more commonly, some cyanosis. Collateral veins around the shoulder and chest on the affected side start becoming prominent within a few days. If these symptoms are ignored or the patient is not definitively treated, over days the symptoms of heaviness, aching, tightness, and arm swelling will improve and may resolve. These symptoms may be mild or not noticeable at rest after adequate time has gone by but the observant patient will notice that with mild activity involving the upper arm, swelling, heaviness, fatigue, and sweating are easily evident. It is these symptoms and outcomes that one attempts to prevent by prompt treatment and decompression of the thoracic outlet.

It is important to remember that the physical exam findings are dependent upon the time from symptom onset to examination. In the patient with a recent onset (i.e., hours to days), one will expect to see edema, tightness, cyanosis, and symptoms of heaviness and aching, and rarely pain and tenderness. If many days to weeks have elapsed, the exam at rest may show little of these signs. In this case, if one exercises the patient by having them do push-ups in a warm room, one may note more duskiness and prominence of collateral veins. With continued exercise, the patient may complain of pain, particularly in the supraclavicular, pectoral, or axillary regions. Upon cessation of exercise, these signs and symptoms resolve rapidly.

DIAGNOSIS

The diagnosis of spontaneous or effort thrombosis of the axillosubclavian vein is not a subtle endeavour. The symptoms as just described are the most prominent feature of the presentation of this condition, and the symptoms in conjunction with the proper demographic profile should raise the suspicion of Paget-Schroetter syndrome.

If axillo-subclavian vein thrombosis is suspected, imaging is the next step. In contrast to arterial thrombosis/embolism, the onset of symptoms is more insidious with venous thrombosis. However, if acute thrombosis is suspected, that is, within hours, prompt anticoagulation with heparin is indicated. More often than not though, by the time the patient presents to a physician who can make the correct diagnosis, the elapsed time is more on the order of days rather than hours. Even in this situation, the patient should be anticoagulated with heparin.

The definitive study to confirm the clinical suspicion and facilitate treatment is a contrast venogram. Noninvasive studies such as duplex ultrasound, in my opinion, have little

role in this situation. There are a limited number of published reports on the sensitivity and specificity of ultrasonography in comparison with contrast venography.[12,13] The reported sensitivity and specificity rates vary from 78 to 100% and 82 to 100%, respectively. No studies specifically have addressed interobserver and intraobserver variability, but it is a widely known fact that ultrasonography is operator dependent in daily practice and that some patients may be more difficult to investigate, such as those with very extensive edema or obesity.

The proximal axillo-subclavian vein is difficult to image directly with ultrasound except in the case of a thin, slender individual. MR venography is better at imaging the axillo-subclavian vein and to diagnose the thrombosis, but once again, access into the venous system is going to be necessary for the first step of treatment. In the presence of clinical suspicion (i.e., a sudden onset of swelling, aching, heaviness), cyanosis and pain in one arm is venous thrombosis until proven otherwise. I would submit that even with a negative duplex, unless the vein was clearly imaged throughout its course, the chances of a false negative duplex ultrasound should make contrast venography the definitive study that allows for diagnosis and treatment.

In addition to being the gold standard, contrast venography is a seamless road to the next step of therapy, namely, catheter-directed thrombolysis of the clotted vein. Prior to the advent of and the demonstrated safety and efficacy of catheter-directed thrombolysis, the treatment of these patients primarily would be surgical thrombectomy with its associated high rethrombosis rates or warfarin anticoagulation.

In a recent paper from the United Kingdom, the authors reviewed their experience with Paget-Schroetter syndrome in four district hospitals.[14] The majority of these patients were treated by nonsurgeons and were treated with warfarin anticoagulation. This treatment strategy was rewarded with a 33% rate of persisting disability—in the authors' estimation, an unacceptably high rate in this era. These results are not dissimilar to the outcomes noted before the use of thrombolysis and thoracic outlet decompression.

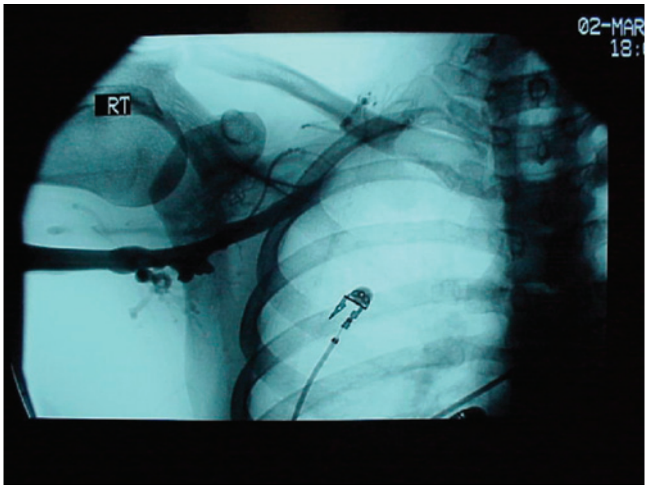

FIGURE 52.1 Venogram of a patient with less than 12 hours of symptoms of arm swelling, aching, and heaviness. The venogram shows abrupt cutoff of contrast with no visible collateral venous channels suggesting an acute thrombosis of the axillo-subclavian vein.

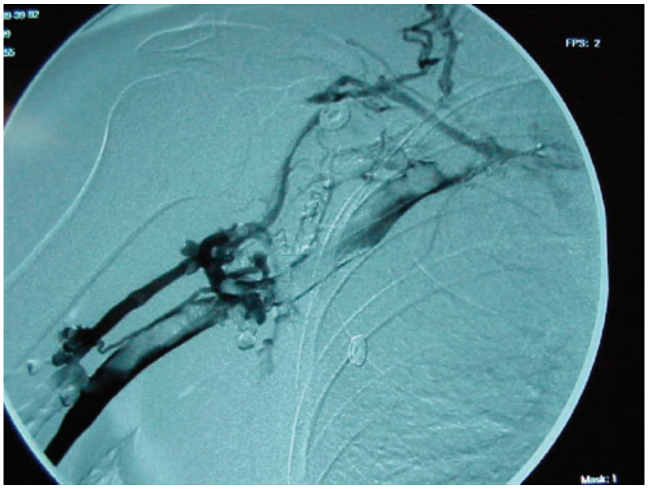

FIGURE 52.2 Venogram of an 18-year-old swimmer with 6 hours of onset of acute arm swelling, pain, and dusky discoloration, which reveals extensive thrombosis of the axillary and subclavian veins.

VENOGRAPHY

Diagnostic venography is performed by accessing the antecubital veins on the affected side. The patient is supine and the venogram is performed ideally with the arm at the patient's side and with the arm at right angles to the chest wall. Figures 52.1 and 52.2 demonstrate the venograms of patients with acute axillo-subclavian vein thrombosis. By contrast, Figure 52.2 shows a venogram with long-standing venous thrombosis of the axillo-subclavian vein. Note the extensive collateralization around the shoulder joint.

TREATMENT

Thrombolysis

The contrast venogram confirms the diagnosis of Paget-Schroetter syndrome and allows for immediate treatment. Once the thrombosis is confirmed, an infusion catheter can be positioned into the vein and thrombolytic therapy can be initiated. The thrombolytic agent of choice in the 1990s used to be urokinase but due to the withdrawal of urokinase from the market in the late 1990s, a new experience was gained

with the use of alternative agents such as tissue plasminogen activator (tPA) and reteplase (Retevase). Urokinase has since been reintroduced into the market but all these agents have proven to be safe and efficacious. Urokinase can be administered at doses of 125,000 U to 250,000 U/hr. tPA is administered at an initial dose of anywhere from 1.5 to 3.3 mg/hr and reteplase is administered at doses of 0.5 to 1 U/hr. Typically, the period of lytic therapy is less than 24 hours but if the clot is of a longer duration, then longer infusion times are necessary.

Lytic therapy allows for complete clot lysis with minimal trauma to the venous endothelium compared to surgical thrombectomy. Upon completion of lysis, one may see a stricture of the vein due to extrinsic compression in the thoracic outlet. The temptation to perform a balloon angioplasty at this time must be strongly resisted. The reason is that until and unless the thoracic outlet is decompressed and the causative compression relieved, balloon angioplasty is destined to fail. Similarly, placement of a venous stent at this time is also to be strongly condemned as it is doomed to failure. Urschel et al. reported on a series of patients with Paget-Schroetter syndrome treated at outside hospitals with lysis and intravenous stent placement without operative decompression of the thoracic outlet.[15] Out of 22 patients treated thus, 22 patients reoccluded their vein from one day to six weeks after stent placement. This is an illustration of a treatment that is not only *not* successful, but is to be condemned in light of the fact that patients treated optimally have such a good outcome following lysis and first rib resection.

TREATMENT FOLLOWING THROMBOLYSIS

Following successful thrombolysis, one is faced with either a patient with a patent axillo-subclavian vein with luminal narrowing due to extrinsic compression or stricture due to long-standing extrinsic narrowing, or a patient with a widely patent axillo-subclavian vein with no stenosis or with stenosis only in the stressed, arm abducted position. Certainly, if there is evidence of venous stenosis after thrombolysis, it is *prima facie* evidence of the fact that compression of the axillo-subclavian vein is due to thoracic outlet compression and accordingly, operative decompression of the thoracic outlet should be performed. If the axillo-subclavian vein following thrombolysis appears to be widely with patent without any evidence of stenosis in the neutral position, the vein should be studied in the stressed position. The provocative maneuvers employed can be any or all of the following:

- Abduction and external rotation
- Arm overhead
- Arm pulled down to the side

If vein compression with any or all of these maneuvers is noted, we would recommend first rib resection with subtotal scalenectomy. If no vein compression is noted with any of these maneuvers, then the decision becomes a little more difficult. Although it is perfectly defensible to anticoagulate the patients for three to six months, first rib resection still should be considered since it is still the most likely cause of spontaneous thrombosis of the axillo-subclavian vein in an otherwise normal healthy patient.

TIMING OF OPERATIVE THERAPY

Thrombolysis results in recanalization of the vein and relief of arm swelling, aching, heaviness, and other symptoms. Until a few years ago, the maxim was that following lytic therapy, the patient should be anticoagulated for four to six weeks with warfarin, and after this time had passed, a transaxillary first rib resection would be performed. This algorithm was based more on a theoretical consideration of the perivenous inflammation rather than any data suggesting that early rib resection was hazardous. This algorithm was challenged by a number of groups performing early first rib resection with equal safety, and the added benefit of avoiding prolonged warfarin use in these young patients. We reported on the safety of such an approach wherein following thrombolysis, we performed a transaxillary first rib resection on the same admission with no difference in complications or efficacy.[16]

Accordingly, we would now recommend that the patient presenting with acute axillo-subclavian vein thrombosis should have a venogram, lytic therapy, followed by transaxillary first rib resection on the same admission. This approach results in quick and definitive therapy. Recognizing that in a subset of patients (approximately 30%) there will be a residual venous stricture despite decompression of the thoracic outlet due to long-standing extrinsic compression, it is our practice to perform a venogram on all patients approximately two weeks following first rib resection. If a significant stenosis is identified at that time, a percutaneous transluminal angioplasty (PTA) is performed. These lesions respond very nicely to PTA alone and we have not found the use of a stent in this situation necessary. Figure 52.3 demonstrates the venogram of one such patient that had thrombolysis, transaxillary first rib resection, followed by PTA of a venous stenosis two weeks following first rib resection.

OPERATION

In 1966, Roos reported a series of 15 patients treated by removal of the first rib from a transaxillary approach.[17] This was a major milestone as the dramatic superiority of this

FIGURE 52.3 Extensive collateralization around the axillary vein suggesting a more long-standing thrombosis of the axillo-subclavian vein.

technique was widely recognized and quickly accepted. The transaxillary first rib resection is the standard operation for removal of the first thoracic rib. Alternative approaches to the removal of the first rib involve an infraclavicular approach to the anterior first rib and/or a supraclavicular approach to removal of the entire first rib. Some authors have found that there is a higher incidence of brachial plexus injuries with the supraclavicular approach compared to the transaxillary approach.

The transaxillary first rib resection has become the gold standard since its description by Roos in 1966. It provides a rapid and direct approach to the first rib and the incision is discreet and cosmetically appealing. The limitations are that it tends to be an operation in which visualization can be limited due to the fact that one is operating in a cavity with limited visualization, particularly for more than one person. However, with experience, this operation can be done quite easily and with excellent results.

The exact details of the operation can be obtained in a variety of good atlases and will be only briefly described here. The patient is placed in a true lateral position with a pad placed under the other axilla to prevent injury to the brachial plexus. The affected arm is prepped into the field so that it is mobile and the assistant elevates the stockinet clad arm by means of a double wrist lock. The arm elevation/retraction is done on an intermittent basis to prevent arm ischemia and brachial plexus injury.

The incision is made transversely at the lower margin of the axilla between the latissimus dorsi and the pectoralis major. This incision is deepened through the subcutaneous tissues and one reaches the cul-de-sac of fascia that separates the axilla from the thoracic outlet. The view from this incision is such that one sees anteriorly the subclavian vein separated from the subclavian artery by the anterior scalene muscle, with the brachial plexus posterior to the subclavian artery. The anterior scalene is divided sharply and anteriorly. The subclavius muscle and tendon that commonly compress the vein are also divided. The first rib is divided with a bone cutter and the cut edges smoothed appropriately. One can get an excellent view and a complete resection of the first rib through the transaxillary approach. The operation typically takes less than two hours and the patient recovery is excellent. Operative details can be obtained by reading the description of Roos[18] as well as the atlas authored by Valentine and Wind.[9]

INTERMITTENT COMPRESSION OF THE AXILLO-SUBCLAVIAN VEIN

Thoracic outlet compression can also manifest with intermittent signs and symptoms of arm swelling, aching, pain, and heaviness that resolve within minutes of onset of symptoms. This phenomenon is termed McLeery's syndrome and represents a variant of venous thoracic outlet syndrome. All the clinical and anatomic features of Paget-Schroetter syndrome are present, and it is only distinguished by the fact that the vein has not proceeded to thrombosis. The treatment for this condition should be the same, namely, first rib resection for decompression of the thoracic outlet. Following first rib resection, the patient should undergo venography to ensure that there is no underlying venous stenosis and if there is, PTA of the vein should be performed.

THE ISSUE OF THE CONTRALATERAL VEIN

In the UCLA series, 61% of patients studied with bilateral venography had thrombosis of compression of the contralateral vein.[11] This is the impetus for the recommendation that the patient presenting with symptoms on one side should undergo venography of the contralateral side. Out of 41 patients studied, 20 patients demonstrated compression and stricture of the contralateral vein, that is, "the unaffected side," in the neutral position and another five patients had evidence of hemodynamically significant compression in the stress position. For this reason, the patient presenting with venous TOS symptoms on one side should have the other side studied and electively repaired by undergoing first rib resection with subtotal scalenectomy.

RESULTS OF TREATMENT

Elman recently published the results of a review of the literature to ascertain the outcomes of patients with upper extremity deep venous thrombosis. The frequency of

post-thrombotic syndrome (PTS) after upper extremity deep venous thrombosis ranged from 7 to 46% and residual thrombosis and axillo-subclavian vein thrombosis appeared to be associated with an increased risk of PTS.[19] In addition, quality of life was impaired in patients with upper extremity PTS, especially after venous thrombosis of the upper arm. For this reason, dissolution of venous clot and decompression of the thoracic outlet must be viewed as an imperative.

The results of first rib resection in the context of the algorithm just discussed are very good. In Machleder's series, 50 consecutive patients were entered into a sequential treatment program for spontaneous axillary-subclavian vein thrombosis.[20] Forty-three had initial thrombolytic or anticoagulant treatment followed by longer-term warfarin treatment. This paper preceded the evolution of the treatment algorithm wherein first rib resection was performed right away on the same admission following thrombolysis. Thirty-six (72%) underwent surgical correction of the underlying structural abnormality, and nine patients had postoperative balloon angioplasty. Ninety-three percent of patients with a patent vein and 64% of those with an occluded vein were essentially free of symptoms. After surgical correction there were no episodes of recurrent thrombosis in a mean follow-up period of 3.1 years. Urschel reported a large series of patients with thoracic outlet syndrome, a subset of whom were patients with venous TOS or Paget-Schroetter syndrome.[21] Long-term results indicated that 205 extremities had good results (the patient returned to work without symptoms). Twenty-four patients had fair results (intermittent swelling but able to work), and 11 patients had poor results (chronic swelling). Seven of the poor results occurred in the 35 patients seen initially more than three months after the thrombotic episode. No patient had phlegmasia cerulea dolens. There were no deaths. These results were in marked contrast to those of 35 patients treated with only anticoagulants: 10 good results, 16 fair results, and 9 poor results. Urschel's data provides the exclamation point for a series of reports from other institutions that attest to the good outcomes following this method of diagnosis and treatment.

CONCLUSION

In our opinion, conservative, read nonoperative, management for this patient population represents suboptimal treatment and operative decompression results in better clinical results, better quality of life, and definitive treatment with very low recurrence rates. This illustrates the reason why prompt lysis and first rib resection should be considered the treatment of choice for Paget–Schroetter syndrome.

Paget–Schroetter syndrome is a disabling condition that tends to afflict the young and active and results in considerable long-term compromise of quality of life and disabling symptoms if appropriate and definitive treatment as described earlier is not undertaken. Prompt thrombolysis followed by first rib resection is the treatment of choice for patients with venous TOS that present with thrombosis or with McLeery's syndrome. The transaxillary first rib resection as described by Roos is the gold standard but anterior approach via a supraclavicular and/or infraclavicular approach also can be used. PTA of the vein should not be undertaken unless the thoracic outlet is surgically decompressed. Venous stents are virtually never necessary as PTA alone in our experience results in long-term venous patency as attested to by the earlier results. A majority of patients will have venous compression in the thoracic outlet on the contralateral side. Prophylactic first rib resection is recommended for the contralateral side on an elective basis. The evolution of the treatment of Paget-Schroetter syndrome has evolved over the last two decades and as it stands, prompt thrombolysis and early first rib resection (same hospital admission) is associated with very good results and represents the optimal therapy for this condition.

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C H A P T E R

53

Subclavian Vein Obstruction: Techniques for Repair and Bypass

RICHARD J. SANDERS

Subclavian vein obstruction, also called venous thoracic outlet syndrome (venous TOS) can be partial or complete. Partial obstruction is due to stenosis; complete obstruction is usually due to thrombosis.

ETIOLOGY

The two categories of causes are primary and secondary. *Primary* subclavian vein obstruction is due to congenital narrowing of the vein at the point where the vein enters the mediastinum just proximal to being joined by the jugular vein. This point lies on the inner aspect of the first rib and is bounded medially by the costoclavicular ligament and superiorly by the subclavius tendon (see Figure 53.1). In most people with narrowing at this point, it may only be demonstrable when the arm is elevated; it appears normal with the arm at the side. As many as 20% of the population have been demonstrated by dynamic venography to have significant narrowing in this area.[1] Fortunately, only a small fraction of these people ever become symptomatic. It is postulated that those who become symptomatic do so because of repetitive movement with the arm in elevated positions causing chronic irritation and fibrosis of the intima in the critical area. Thus, stenosis may be the first pathologic step, which may or may not be followed by thrombosis. Primary subclavian vein thrombosis is also called effort thrombosis, idiopathic thrombosis, or Paget-von Schroetter syndrome. The cause of primary subclavian vein obstruction is always *extrinsic* to the vein.

Secondary subclavian vein obstruction is due to known causes such as tumor, coagulopathy, or iatrogenic factors like catheters or wires. Subclavian vein catheters are by far the most common cause of subclavian vein obstruction and thrombosis. For some unknown reason thrombosis from such catheters seldom causes severe enough symptoms to require any treatment other than anticoagulants. With the exception of tumors, the causes of secondary subclavian vein obstruction are always *intrinsic*.

SIGNS AND SYMPTOMS

Swelling of the entire arm is the primary symptom. Swelling limited to the fingers and hand can occur with neurogenic thoracic outlet syndrome and is not indicative of venous obstruction unless the whole arm is involved. Other symptoms are cyanosis, a feeling of fullness, aching, or pain. Some patients have mild paresthesia.

Physical examination confirms the swelling and cyanosis. The only other significant finding is dilated subcutaneous veins over the shoulder and upper chest wall of the affected side.

DIAGNOSIS

The two diagnostic tools in use today are duplex scanning and venography. Venous pressure measurements also can be used, but these are cumbersome and unreliable unless there is obvious arm swelling. Duplex scanning requires an experienced technician because the clavicle lies directly over the critical part of the subclavian vein. Though duplex scanning is fairly reliable for total occlusion of the vein, accurate diagnosis of stenosis without thrombosis is difficult. Venography remains the gold standard for evaluating the subclavian vein. A venogram with the arm at rest is usually enough to make the diagnosis of total occlusion, but subclavian vein

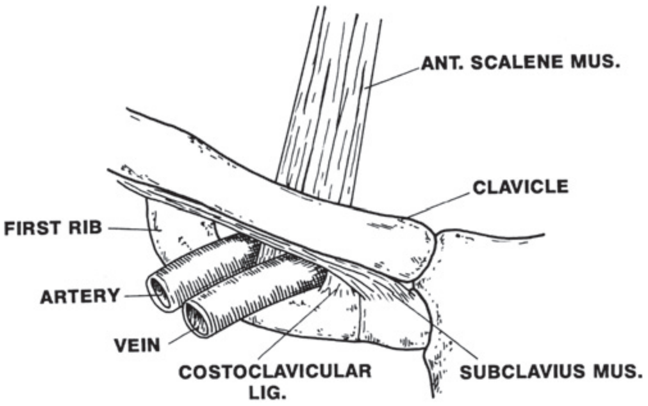

FIGURE 53.1 Anatomy of the costoclavicular space. The subclavian vein can easily contact the costoclavicular ligament, subclavius muscle, clavicle, first rib, or anterior scalene muscle. Reprinted with permission from Reference 15.

stenosis may be demonstrable only with dynamic positioning, elevating the arm to 90 degrees and 180 degrees.

TREATMENT

The approach to managing subclavian vein obstruction is threefold:

1. Remove the thrombus. For recent thrombus, thrombolysis or thrombus extraction with appropriate devices is always the first step. If unsuccessful, surgical thrombectomy can be considered.
2. Remove the extrinsic cause. First rib resection with venolysis is the primary procedure for treating the underlying cause. This should follow removal of the thrombus when dealing with thrombosis, but this is the only treatment needed for nonthrombotic subclavian vein obstruction. Adequate thrombolysis can be achieved through transaxillary or infraclavicular approaches. In most patients, the supraclavicular route does not provide adequate exposure to divide all the ligaments and totally free the vein. In reports where the supraclavicular route has been tried, the majority of patients also required an additional infraclavicular incision to complete the operation.[2,3,4] Thus, unless the supraclavicular route is needed to treat neurogenic TOS, venous decompression is best performed through the other approaches.
3. Remove the intrinsic obstruction. Treatment of the internal venous obstruction should be considered only after the first two steps have been completed. In the large majority of patients with subclavian vein obstruction, symptoms will be completely or almost completely relieved once the thrombus has been removed and the subclavian vein decompressed by rib resection and venolysis. Thus, no further treatment is needed. Only in patients who continue to have significant swelling and pain is venous reconstruction indicated.

There are three approaches to relieving intrinsic subclavian vein obstruction:

- Balloon angioplasty
- Endovenectomy with vein patch
- Subclavian vein bypass

Balloon Angioplasty

Percutaneous balloon angioplasty (PTA) is usually successful in treating stenosis when performed after the subclavian vein has been decompressed by resection of the first rib and the attached ligaments. Prior to first rib resection, the extrinsic pressure around the vein prevents its expansion, making PTA ineffective. Studies of PTA performed prior to rib resection have revealed not only uniform failure but in several patients, rethrombosis was precipitated by the attempt.[5]

More than one center has followed a protocol of routine balloon angioplasty in those patients with residual stenosis either immediately after rib resection in the operating room suite, or within 24 hours of rib resection in the angio suite.[4,6] The results have been successful in over 90% of the patients. This certainly raises the question of whether or not this should be used in all patients with residual stenosis following surgical decompression. However, in our experience, we have not found it necessary to use PTA routinely on all postoperative stenoses, although we do use it on tight stenoses with collaterals as seen on resting venograms. Patients with stenosis of less than 80 to 90% have been followed and if symptoms of swelling and aching persist, PTA is performed. This protocol has been quite successful as seldom have patients with residual post-operative stenosis been symptomatic and required additional treatment.

Endovenectomy with Vein Patch

If thrombolysis has been incomplete and residual thrombus or tight stenosis remains, two approaches may be employed. Either proceed with first rib resection and venolysis, followed by PTA, or consider opening the vein, performing surgical thrombectomy, endovenectomy, and closing the venotomy with a vein patch graft. The same technique also has been applied to total occlusion of less than 2 cm.[7] Unfortunately, in some patients adequate proximal venous control cannot be obtained without opening the mediastinum. A median sternotomy down to the first interspace and then a transverse incision into the interspace will free enough of the manubrium to elevate the clavicle and provide excellent

exposure for the procedure.[8] Although we have had 100% success with this technique in 11 patients, it is an extensive procedure requiring several weeks to completely recover from the operation. It makes sense to try PTA first if at all possible. Endovenectomy can be performed a day or two later if PTA fails.

Endovenectomy is performed via a 12- to 14-cm infraclavicular incision, splitting the pectoralis major fibers between sternal and clavicular heads, and mobilizing the subclavian vein. If the first rib is still present, it is now excised, dividing the anterior end at the costal cartilage then removing as much additional cartilage and manubrium as needed to expose the subclavian vein as far medial as possible. The subclavian vein is palpated to locate the proximal end of the thickened vein. If the proximal vascular clamp can be applied on thin, soft vein, no further exposure is needed. If the proximal vein cannot be reached because of the overhanging sternum, the trap door sternal flap of Molina through the first interspace is created to expose the subclavian-innominate junction (see Figure 53.2).

Following distal and proximal control, the patient is heparinized and a venotomy performed over the thickened venous segment. Thrombectomy is performed first, removing all organized clot proximal and distal to the venotomy with embolectomy forceps. Thickened, organized clot that is firmly adherent to the intima cannot be removed with embolectomy forceps. This often has the appearance of a tumor inside the vein. This must be excised sharply with scissors or a knife, leaving a small rim of clot remaining against venous intima. It is impossible to find a smooth plane of dissection in the vein wall as is done with arterial endarterectomy. When this is attempted in a vein, the adventitia usually is perforated. It is best to simply leave a 1- to 2-mm thickness of organized clot against the vein wall (see Figure 53.3).

A saphenous vein patch is used to close the venotomy. In most patients, we have left a few centimeters of the saphenous vein graft unopened, in continuity with the distal tip of the patch. The end of this vein is then sewn to

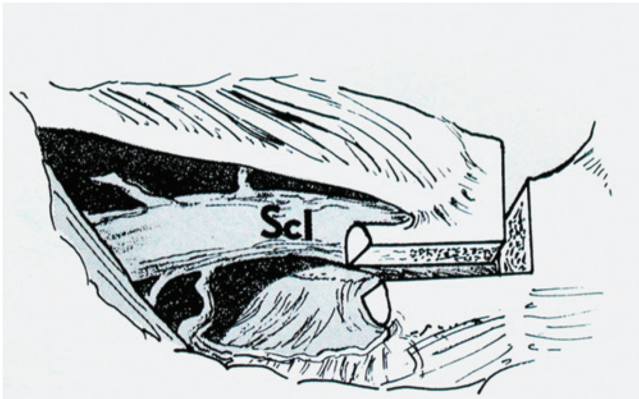

FIGURE 53.2 Technique of sternal splinting to first interspace with transverse extension laterally to free the clavicle with a small piece of sternum attached. This provides excellent exposure of subclavian-innominate junction. Repair is with two or three sutures of heavy Dacron or wire. Reprinted with permission from Reference 8.

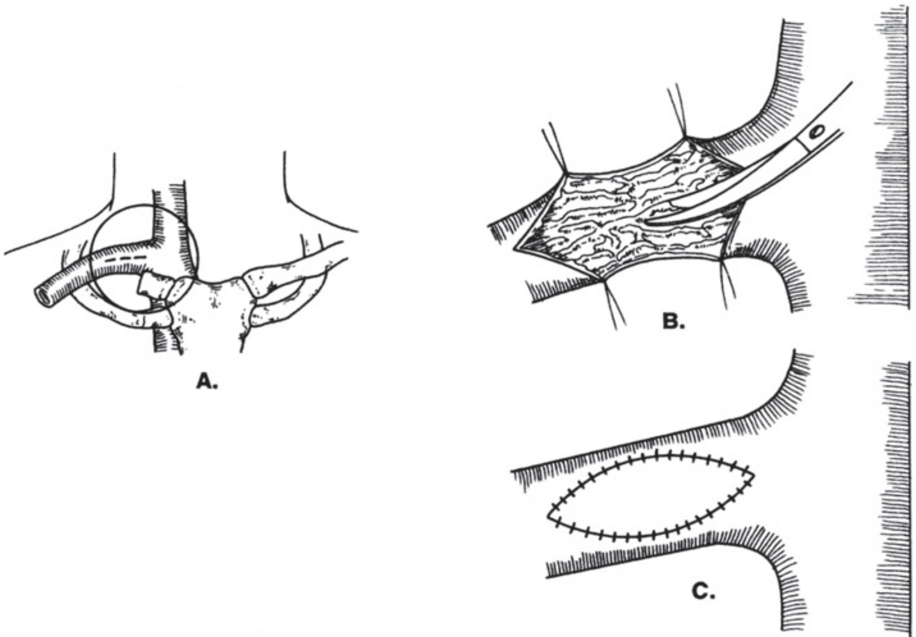

FIGURE 53.3 Technique of endovenectomy of the subclavian-innominate junction and patch graft with autogenous vein. Reprinted with permission from Sanders RJ. Management of subclavian vein obstruction. In Bergan JJ, Kistner RL, eds. Atlas of venous surgery. Philadelphia, PA: WB Saunders; 1992: 267.

the side of the axillary artery to create a temporary arteriovenous fistula (AVF) that will flow directly over the endovenectomy segment. This is done to prevent postoperative thrombosis of the repair, which tends to occur in low pressure systems when a fresh, rough surface has been left in the vein.[9]

The fistula can be closed two to three months later. Because it can be very difficult to find the AVF at this time, we place a 2-0 or 3-0 Prolene suture loosely around the AVF to aid closing it (going through the same skin incision). By placing the suture doubly around the AVF, it can be pulled up and tied so that the vein itself does not requiring dissecting out. Because the ends of the suture are usually difficult to find, leaving the ends of the suture long and bringing them up into the subcutaneous tissue over a button will make them easier to find. An alternative to this is to create a temporary AVF in the ipsilateral arm. In dialysis patients who already have a functioning AVF in the ipsilateral arm, another AVF is unnecessary.

Subclavian Vein Bypass

Indications

When subclavian vein thrombosis cannot be resolved, total occlusion becomes a chronic problem. Treatment is indicated only for significant symptoms of swelling and pain. Patients whose veins cannot be opened by thrombolytic therapy should be anticoagulated for several months and followed. Many patients will recanalize without additional treatment. Among those who remain occluded, the majority will enjoy symptomatic improvement over the next six to 12 months by the development of adequate collaterals. In one study of 95 patients treated only with anticoagulants, 60% were totally asymptomatic or had minimal symptoms, 27% had symptoms only with moderate exercise, and only 13% were symptomatic at rest.[10]

Choice of Bypass

Venography is necessary to determine the type of bypass to perform. For occlusions limited to 5 to 6 cm, with good inflow, axillojugular vein transposition is our procedure of choice. This procedure is limited to short occlusions. For longer occlusions, the jugular vein will not reach the more distal axillary vein and some type of graft must be used. Aortic homografts,[8] saphenous vein spiral[11] or panel grafts, prosthetic materials, and even transposition of the contralateral cephalic vein sewn to the brachial or axillary vein[12] all have been successful. Because subclavian vein bypass is seldom needed there is no large database to help one choose the best graft material. In dialysis patients who already have a functioning AVF, the easiest bypass is with a prosthesis from the axillary to the internal jugular vein. Although this is prosthetic material, the AVF will usually maintain high enough pressure and flow to prevent thrombosis.[13]

Technique of Juguloaxillary Vein Bypass

The technique is described in Figure 53.4. An infraclavicular incision 2 to 3 cm below the mid-clavicle is used. The pectoralis major is split between clavicular and sternal heads. The pectoralis minor tendon is divided and the axillary and subclavian veins mobilized and surrounded with vessel loops. Two transverse incisions are made in the neck to dissect the internal jugular vein. The first is 2 cm above the clavicle, 5- to 6-cm long, and directly over the sternocleidomastoid muscle. The sternal and clavicular heads of this muscle are split and the internal jugular vein dissected circumferentially and surrounded with a Penrose drain. The vein is totally freed as far as possible both proximally and distally by dividing all bands. A second incision, 4- to 5-cm long, is made below the mandible. Through this incision the cephalic portion of jugular vein is freed proximally to the base of the skull and distally to meet the freed portion of vein in the tunnel between the two incisions.

A tunnel is created behind the clavicle between the subclavian vein and the supraclavicular incision. The subclavius muscle is divided and a kidney pedicle clamp passed between the two incisions. The tunnel is dilated bluntly so that the jugular vein can pass easily through it without compression in the tunnel. The jugular vein is marked with a stitch on its anterior wall for orientation. The vein is clamped and divided close to the base of the skull. The cephalic end is suture ligated. The distal end is carefully passed down the jugular tunnel, brought out through the lower neck incision, and freed as far as possible below the clavicle up to the subclavian vein junction. The vein is then passed though the tunnel beneath the clavicle. The patient is heparinized and a longitudinal venotomy is performed, excising a narrow rim of the vein wall. Passing a 12 to 14 French catheter through the vein prior to performing the anastomosis is a good way to check that the subclavian vein is unobstructed and not kinked in its path to the innominate vein. An end-to-side anastomosis is performed with 6-0 Prolene. Some surgeons have elected an end-to-end anastomosis; either is effective.

Because venous repairs are subject to thrombosis due to low flow pressures,[9] a temporary AVF is created between the axillary vein and axillary artery, provided there is adequate room on the axillary vein distal to the anastomosis. We have used ringed or spiral reinforced 6-mm PTFE for the AVF. This is placed in a loop that comes up into the subcutaneous tissue to make it easier to find when the

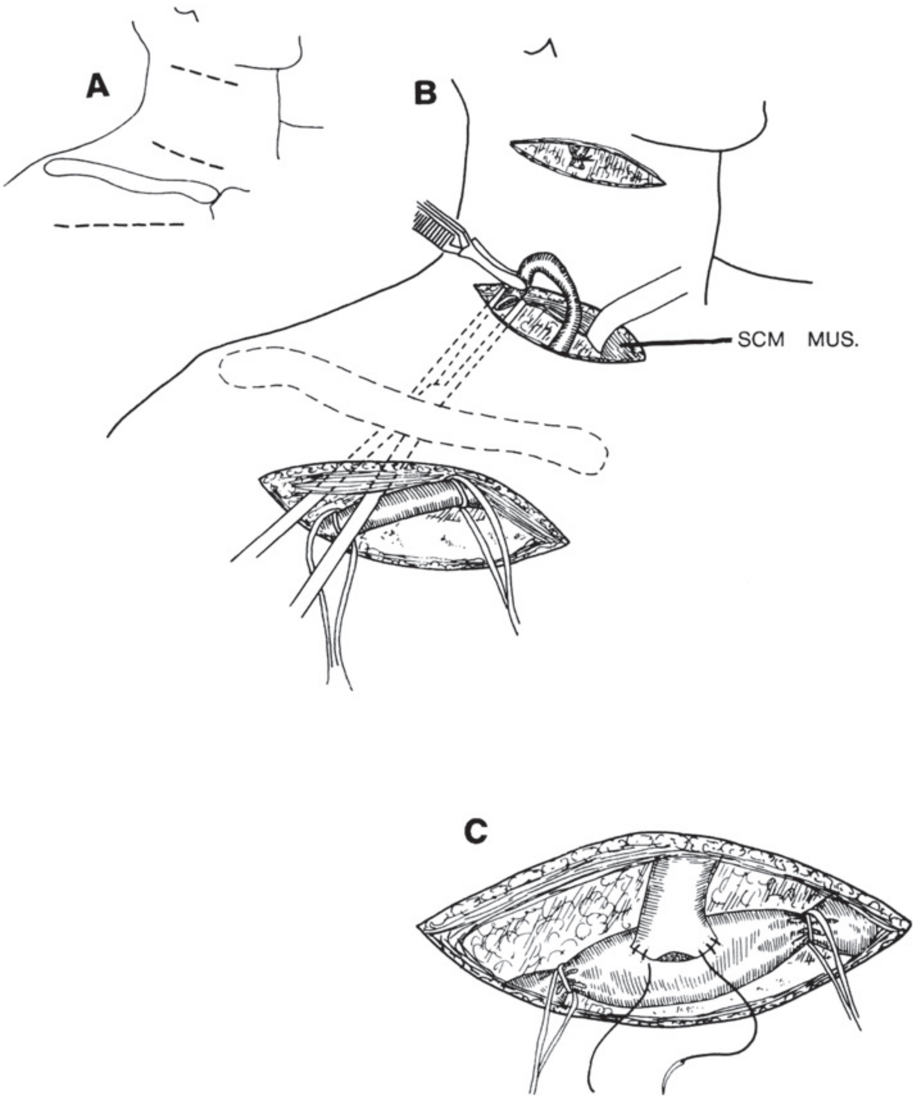

FIGURE 53.4 Technique of jugulosubclavian vein bypass. Reprinted with permission from Reference 15.

temporary AVF is taken down. We usually remove the AVF in about three months.[14] An alternative AVF can be created in the arm or antecubital space if creating it between axillary vessels appears too difficult.

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C H A P T E R

54

The Primary Cause of Chronic Venous Insufficiency

MICHEL PERRIN

BACKGROUND

Definition

Primary venous insufficiency (PVI) is chronic venous dysfunction whose cause is neither congenital nor clearly identifiable. By restricting our attention to CEAP (clinical, etiological anatomical, pathophysiological) classes C4–C6, only patients that present chronic skin or subcutaneous lesions including healed and active ulcer are to be discussed, and we will limit our focus to the primary cause of these problems.

History

For a long time C4–C6 classes were supposed to be secondary (postthrombotic), but at the present time we know, thanks to ultrasound investigations, that primary etiology is common in patients classified as C4–C6.

One of the major merits of the CEAP classification has been to take in account the etiology, information that was missing in previous classifications.

In the updated CEAP,[1] another credit has been added, the use of the advanced CEAP. In the advanced CEAP all the signs listed in the C classes have to be reported. For example, a patient presenting with reticular veins, varices, edema, pigmentation, and active ulcer will be quoted C1, 2, 3, 4a, 6. In the problem that we are dealing with in this chapter the descriptor etiology will always be primary, the descriptor anatomy will inform what venous system is abnormal: superficial, deep, perforator, and their possible combinations. Last, the descriptor physiopathology will provide information on the physiologic anomaly that was identified in the 18 veins or groups of veins listed in the descriptor anatomy. For example a patient presenting reflux in the great saphenous vein above and below the knee, the small saphenous vein and the calf perforators will be described when using the advanced CEAP as follows: As, p, P r 2, 3, 4, 18.

If we return to the patient described earlier in terms of clinical and etiologic descriptors and if we add the anatomical and physiopathological descriptors, he will be quoted C1, 2, 3, 4a, 6, Ep, As, p, P r 2, 3, 4, 18. But we know that some patients may have a primary reflux below the inguinal ligament combined with superficial and perforator reflux. If in the same symptomatic patient, this reflux is identified in the common femoral, deep femoral, femoral, popliteal, and crural veins, the patient will be described C1, 2, 3, 4a, 6 s, Ep, As, p, d, P r 2, 3, 4, 11, 12, 13, 14, 15, 18. As it was published only recently, the advanced CEAP has not yet been used for epidemiological studies, where it should be a very useful tool.

EPIDEMIOLOGIC STUDIES

Only recent epidemiologic studies will be analyzed. Some studies give the prevalence of C4–C6 in the general adult population.[2–5] This information is displayed in Table 54.1, but in these studies no data were provided concerning relationships between etiology and clinical class.

COHORT STUDIES

Until now precise information on the etiology, anatomic, or physiopathologic abnormalities have been available only in C5–C6 patients.

Analyzing 182 legs presenting chronic venous ulcers (C5–C6) examined by duplex color scanning (DCS), Magnusson[6] identified a primary etiology in 127 (69.8%)

TABLE 54.1 Prevalence of C4–C6 Patients

Study First author	Population studied (Number) Age	Classification used to identify clinical status	Prevalence
San Diego Population Study Criqui (2)	Cross-sectional study University employees active or retired (2211) ?	CEAP C4–C6	6.2%
Edinburgh Vein Study* Evans (3)	Cross-sectional population study Edinburgh residents (1566) 16–84	Widmer clinical classes CVI 2 = C 4 in the CEAP CVI 3 = C 5–6 in the CEAP	M = 2.3% F = 1.3%
Polish Study Jawien (4)	Cross-sectional population study Polish adults rural (21%) and urban area seeking medical help regardless of the cause (40,095) ?	CEAP C4–C6	5.1%
Bonn Study Pannier (5)	Cross-sectional population study Bonn and rural respondents (3072) 18–64	CEAP C4–C6	3.6%

*In the Edinburgh Vein Study ankle flare was used to qualify CVI 1, but as this sign is not listed in the CEAP classification, prevalence numbers might be distorted.

and secondary in 55 (30.2%). Among the primary patients 62 (49%) had only superficial insufficiency, 45 (35%) a combination of deep and superficial reflux, 14 (11%) deep reflux alone (half of them in this subgroup had previously undergone saphenous vein surgery), and 6 (5%) had no identifiable reflux. It is worth noting that in the various groups incompetent calf perforators were observed in 44, 64, 43, and 0%, respectively.

MacDaniel[7] used DCS examination and air plethysmography (APG) in examining 99 ulcerated legs (C6). Sixty-four percent of the patients had a primary etiology and 36% secondary.

In another series of 111 C5–C6 legs,[8] 57 (51%) had only superficial incompetence, which means that the etiology was primary. But it must be kept in mind that in the group with isolated deep incompetence, 6 legs (5%) and the combination of deep and superficial in 42 (44%), the deep venous reflux was probably primary. This probability is supported by the fact that only 20 legs were listed as suspected (14) or proven deep (6) vein thrombosis.

Tassiopoulos[9] reviewed 13 studies reported between 1980 and 1998, which used DCS to assess 1249 limbs with chronic venous ulceration. The incidence of previous DVT was 32% (95% CI 27–36) in 405 limbs where this information was documented. Ninety-two percent of the 1249 limbs assessed demonstrated venous reflux with isolated superficial venous reflux present in 45% and combined deep and superficial reflux present in 43% of the limbs.

Relationship between deep vein posthrombotic reflux identified by DCS and C4–C6 class was established in a series of 97 patients[10] (C4: 24.5%, C5: 31.8%, C6: 34.4%).

TABLE 54.2 Pattern of Venous Reflux in 496 Limbs with Chronic Venous Ulceration (adapted from Reference 11)

Patterns of reflux	Number of limbs	Percentage
Isolated SVR	230	46.4
SVR + IPVs	28	5.6
SVR + sDVR	54	10.9
SVR + sDVR + IPVs	9	1.8
SVR + f-l DVR	88	17.7
SVR + f-l DVR + IPVs	21	4.2
Isolated f-l DVR	49	10.0
Isolated sDVR	7	1.4
Isolated IPVs	2	0.4
f-l DVR + IPVs	7	1.4
sDVR + IPVs	1	0.2

Abbreviations: SVR = superficial venous reflux; IPVs = incompetent calf perforating veins; sDVR = segmental deep venous reflux was defined as deep venous incompetence in the presence of at least one competent deep vein valve above or below the refluxing segment knowing that three venous segments were investigated, the femoral, the below-knee popliteal, and the gastrocnemius veins; f-l DVR = full-length deep venous reflux.

Another study gives the pattern of venous reflux in 496 limbs (C5–C6)[11] (see Table 54.2). Again it must be underlined that obviously some patients in the two last series had a combination of primary superficial and deep venous reflux.

Nevertheless there is another series in which results concerning the patterns of reflux are noticeably different.[12] One hundred and seventy C4–C6 legs were compared with 274 C0s–C3. The most obvious difference between the two groups was the presence of an axial deep reflux in the C4–C6

group (OR, 2.7; CI 1.56–4.57). In contrast, presence of axial reflux* in superficial veins did not increase prevalence of skin changes (OR 0.73; CI 0.44–1.2). The authors concluded that continuous axial deep venous reflux is a major contributor to increased prevalence of skin changes or ulcer with chronic venous disease compared with segmental deep venous reflux above or below the knee. Information on etiology was reported on the whole group: Ep 302 legs (75%), Es 99 legs (25%), but not per class.

In a very well-documented series[13] of 98 limbs graded C6, 66 extremities (67%) were primary. Superficial reflux with or without involvement of other systems was seen in 84 extremities (86%), incompetent perforators were identified in 79 limbs (81%), and 72 legs (73%) had deep reflux with or without involvement of other systems.

In the deep reflux subgroup, 22 extremities out of 72 had a reflux grades 3 and 4 according to Kistner classification[14] (grade 3 = 7; grade 4 = 15). It is worth noting that all patients with a reflux grade 4 had a combination of superficial and/or perforator insufficiency (10 superficial + perforator, 4 isolated superficial, 1 isolated perforator). Nevertheless six legs had no axial superficial reflux.

From all these studies it is clearly established at present that in patients classified C4–C6 primary etiology is at least as frequent as secondary etiology. This statement leads to practical management.

MANAGEMENT OF C4–C6 PATIENTS

For some authors,[15,16] only patients who have chronic changes in the skin and subcutaneous tissues of the lower leg deserve to be referred to clinically as chronic venous insufficiency (CVI). This definition, also generally accepted, is used in this chapter, but in the updated CEAP[1] C3 patients have been included in CVI.

CVI is an expression of severity in chronic venous disease, therefore management guidelines for CVI patients need to be stated both in terms of investigations and treatment.

Investigations

Besides clinical examination all C4–C6 patients must be investigated on level II as defined in the revision of the CEAP,[1] which means mandatory DCS. In most cases, that allows documentation for the advanced CEAP classification. In other words, the physical signs, absence or presence of symptoms, etiology, and anatomic and physiopathologic abnormalities are all clearly identified. It is essential to know in every anatomical system—superficial, deep, and perforator—what veins are obstructed or refluxing and what etiology is identified: primary, secondary, congenital, or traumatic.

In patients with CVI we recommend complementing the CEAP classification by using the venous severity scoring system[17]—we know that in patients with C4–C6, the three scoring systems, venous clinical severity score (VCSS), venous segmental disease score (VSDS), and the venous disability score (VDS) are particularly useful. To fulfill the VSDS, complementary investigations are needed occasionally, such as venography, venous helical CT scan, magnetic resonance imaging, and so on, according to the venous disease type.

Quantifying the global CVI severity investigations such as ambulatory venous pressure (AVP) and APG may be useful.

Treatment

Methods of Treatment

The various treatment methods will not be described in this chapter because they are detailed in others. They can basically be divided into two groups: conservative and invasive. The first includes compression, drugs, and physiotherapy; the second includes sclerotherapy, open surgery, and endovascular surgery. The main difference between the two is very important to keep in mind. Conservative treatment usually is prescribed regardless of the etiology, the anatomical and physiopathological anomaly.

On the contrary invasive treatments selectively take into account etiology, anatomic lesions, and physiopathologic disorders. Superficial venous reflux can be treated by sclerotherapy, open surgery, and endovascular surgery knowing that the different techniques can be combined.

For treating perforator insufficiency, three techniques are available: sclerotherapy, ligation by open surgery, and subfascial endoscopic perforator surgery (SEPS).

Deep venous surgery is supposed to treat obstruction or reflux. In primary etiology obstruction is not frequent and reflux common. For treating primary deep reflux, valvuloplasty or valve transfer are the most common methods used.

Treatment Results

Since the information concerning the outcome of the various treatments is provided elsewhere in this volume, we will focus on patients C4–C6 with PVI.

Surprisingly very few studies give precise information both on the clinical class and etiology in this situation except

*Axial reflux was defined as reflux in the Great Saphenous vein above and below the knee or in the femoral vein to the popliteal vein below the knee.

for patient C5–C6. Only controlled randomized trials (RCTs) with few exceptions will be analyzed.

Compression

C4a (eczema, pigmentation). There are no RCTs.
C4b (lipodermatosclerosis, atrophie blanche). One RCT[18] has shown that stockings improve lipodermatosclerosis but C4b etiology is not detailed in this study.
C5–C6 (healed ulcer, active ulcer). Many RCTs comparing different bandages are available but the results according to the etiology are not documented.

In two studies compression is compared to surgery.

In the first[19] 75 venous leg ulcers (VLU): 51 of primary etiology (47 isolated superficial venous insufficiency and 14 with a combination of superficial and deep vein reflux), 13 posthrombotic, and one congenital were randomized between minimally invasive surgical hemodynamic correction of reflux (CHIVA is the French acronym for this method) and compression. Healing was shorter in the CHIVA group ($P < 0.02$). At a mean follow-up of three years, the recurrence rate was lower in the CHIVA group ($P < 0.05$) and investigation parameters such as quality of life (QoL) were improved in the operated group. Because primary and secondary etiology were not evaluated separately, the extent of the reflux was not documented, and the number of patients was small.

In the second study,[20] 500 consecutive patients with VLU presenting superficial venous reflux and mixed superficial and deep reflux were randomized in two groups, either compression alone or in combination with superficial venous surgery. Deep venous reflux was assessed in three locations: common femoral or femoral veins, above knee popliteal vein, and below knee popliteal vein. When one or two of the three studied deep segments were refluxing, deep reflux was denominated segmental deep; when the three segments were involved it was classified as total deep.

Primary endpoints were 24-week healing rates and 12-month recurrence rates. Results were analyzed on an intention-to-treat basis. Overall healing rates were similar in both groups.

Results of subgroup analysis showed that the surgery and compression arm with isolated superficial reflux and mixed superficial and segmental deep reflux had lower 12-month recurrence rates (12% vs 26% and 9% vs 25%; $P < 0.0001$ and $P = 0.04$, respectively).

No significant difference in recurrence rate was seen in patients with mixed superficial reflux and total deep reflux (19% vs 31%; $P = 0.42$).

These results are in accordance with Adam's article.[21] In a series of 39 VLU in which superficial and segmental deep reflux were combined, segmental deep reflux resolved in 19 of 39 (49%) limbs, and ulcer healing occurred in 30 of 39 (77%) limbs at 12 months after isolated superficial venous surgery.

Although these studies did not differentiate primary from secondary etiology, their results provide major information that will be very helpful for recommending indications for treatment PVI in C4–C6 patients.

Sclerotherapy

There are no RCTs comparing sclerotherapy versus other treatment in PVI C4–C6 patients.

Open Surgery

Superficial Venous Surgery

In the two RCTs studies previously reported surgery plus compression versus compression alone in C5–C6 patients, only superficial venous surgery was used. In the first one[19] it was the CHIVA technique, that is, high ligation + disconnection of the tributaries from the saphenous trunk. In the second,[20] the procedures were isolated saphenofemoral or saphenofemoral junction disconnection, or combination of junction disconnection, tributary stab avulsion, and saphenous trunk stripping (only for the great saphenous vein).

There are no RCTs for C4 patients comparing surgery to other treatment.

Perforator Surgery

Although SEPS largely has been used for treating C5–C6 patients whatever the etiology, there are no RCTs comparing results of superficial surgery versus superficial surgery + SEPS. In the North American Subfascial Endoscopic Surgery Perforator study[22] (146 patients), SEPS was combined with superficial venous surgery in 103 patients (71%). Patients with primary valvular incompetence had one-year (limbs at risk 41) and two-year (limbs at risk 25) recurrence rates of 15% and 20%, respectively, compared to 47% after two years in those of secondary etiology.

Deep Venous Surgery

As obstruction is not very frequent in PVI, only reflux will be considered. There are no RCTs comparing either conservative treatment versus any kind of surgery including reconstructive surgery for correcting deep venous reflux. Outcomes of this surgery remain difficult to judge because PVI superficial, perforator, and deep reflux are frequently combined; when they are present and treated by surgery all of them are corrected.

Nevertheless in many series treated by deep venous reconstructive surgery conservative treatment or/and venous superficial surgery, perforator ligation had been used previously and were unsuccessful.

In the last large series reported,[23] 118 limbs with nonhealing ulcers (PVI C6) were treated by valvuloplasty. At two-year follow-up, 63.5% ulcers were healed.

In our series[24] the ulcer recurrence free survival was 75% at five years (44 limbs) for PVI (C5–C6) and among the 24 limbs PVI (C4) no ulcer occurred after deep surgery.

Grossly deep valvuloplasty +/– previous or concomitant superficial venous surgery and perforator ligation is credited at five years with 70% good clinical (no ulcer recurrence) and hemodynamic results: competence of the valve(s) repaired.[24]

It is worth noting that in all series treated by valve repair, the deep reflux was an extended axial reflux graded 4 according to Kistner's classification.[14]

Endovenous Surgery

There is no outcome assessment concerning PVI C4–C6 patients.

INDICATIONS

According to the reported results very few recommendations of grade A or B can be given. Most are grade C or consensus agreement.

In the presence of isolated superficial insufficiency the active treatment is strongly recommended. Because there are now no RCTs comparing sclerotherapy to other treatments, surgery is the technique of choice as long as long-term results of foam sclerotherapy are not available. What surgical technique should be used? In presence of major reflux at the saphenofemoral or saphenopopliteal junction, particularly when the terminal valve is incompetent, high ligation-resection of the saphenous junction remains legitimate combined with trunk saphenous stripping and stab avulsion of the incompetent tributaries.

Endovenous surgery does not include ligation resection of the saphenofemoral junction and postoperatively a non-refluxing patent saphenous stump usually is identified at the site of the previous saphenofemoral junction. We don't know what the long-term results should be in the patients who had an incompetent terminal valve with a massive reflux preoperatively. Conversely we know that neovascularization is infrequent after endovenous surgery.

Association of Superficial and Calf Perforator Veins Insufficiency

There is no consensus agreement in this situation. In PVI grade C4, isolated superficial venous surgery, as stipulated in the previous paragraph, is the most frequent choice. If persistent incompetent perforators are identified after surgery, they should be treated by surgery, sclerotherapy, or compression. In C5–C6 the same management is the rule for some phlebologists, but for many vascular surgeons medial incompetent calf perforators should be treated by SEPS at the same operation.

Combination of Superficial Venous Insufficiency +/– Perforator Insufficiency and Deep Venous Reflux

In the presence of a deep segmental or axial reflux graded 1 to 3, venous reconstructive surgery seldom is considered and the patient management is the same as stipulated in the preceding paragraph.

In total deep reflux (i.e., grade 4), there is again no consensus. Phlebologists and some vascular surgeons model their attitude to the one adopted when a segmental reflux is identified. Compression is prescribed after control of superficial and perforator incompetence.

But for others in patients graded C5–C6, deep venous reconstructive surgery must be considered in the absence of contraindications: uncorrectable coagulation disorder or ineffective calf pump. Valvuloplasty (single, multilevel, multisystem) is the most suitable technique, internal for most of the surgeons,[25] external (transcommisural) for Raju and Neglen.[26] Superficial and perforator reflux must be treated at the same time, for some authors as a first step, for others shortly before deep venous surgery in the same hospitalization.

Isolated Primary Deep Vein Reflux

This presentation is not common but C5–C6 or C4b class findings in young patients who are reluctant to wear compression for all their lifetime and with extended deep reflux are candidates for valve reconstruction.

Post-Operative Compression

This problem is not solved. There is no rule for how long a patient must wear elastic compression after any kind of surgery. One must rely on clinical features, other investigations, or both. When there is no more skin or subcutaneous change or when the APG or the photoplethysmography parameters become normal or subnormal, compression should be discarded.

GUIDELINES FOR PROSPECTIVE STUDIES

Many studies should be undertaken in order to provide Grade A or B recommendations.

First of all an epidemiologic survey in the general population is desirable in order to know the prevalence and incidence of PVI in CVI patients and the respective numbers in

the different classes (C4a, 4b, 5, and 6). Besides it would be essential to get in each group the representation of the different anomalies according to the anatomical location: isolated superficial, perforator, and deep vein insufficiency and their various combinations.

Concerning treatment the following studies should be recommended:

- In patients with isolated superficial reflux, RCT comparing foam sclerotherapy versus open surgery and endovenous surgery.
- In patients combining superficial and perforator reflux RCT with two arms is needed: one arm where patients will be treated by superficial venous surgery, the other by a combination of superficial surgery and perforator ligation.
- In patients with deep anomalies RCTs would be difficult to put in place as the number of patients is small and their anatomic and physiopathologic patterns are mixed. Nevertheless long-term follow-up assessing valvuloplasty in patients with axial and extended deep reflux have to be analyzed in detail as the patients selected for deep surgery were failures of the conservative treatment.

CONCLUSIONS

It is presently recognized that PVI is at least as frequent as secondary in CVI. That means that all patients with CVI have to be investigated with DCS to fulfill all the headings of the advanced CEAP classification, but most importantly to identify superficial venous insufficiency. As this isolated anomaly is easily correctible by invasive treatment (surgery, sclerotherapy), it has to be identified.

When perforator incompetence is combined there is presently no consensus for treating them in combination.

Primary deep vein reflux, when axial and extended, needs complementary investigations because valvuloplasty must be considered in the absence of contraindications, particularly in patients not improved by conservative or/and superficial venous +/− perforator surgery.

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CHAPTER

55

Conventional Surgery for Chronic Venous Insufficiency

WILLIAM MARSTON

INTRODUCTION

Successful treatment of patients with symptomatic chronic venous insufficiency (CVI) requires a detailed analysis of the anatomic and physiologic correlates of venous dysfunction. Using this information the physician may determine whether correction of the source of CVI is possible and if so, which procedures may be useful to do so. With the proliferation of minimally invasive procedures in the last decade, conventional surgical correction of venous insufficiency is performed less frequently. However these procedures remain useful in some instances as the primary procedure of choice. Regardless of whether a surgical, endovenous, injection-based, or other procedure is performed, the goal is the same: correction of abnormal venous reflux or obstruction resulting in CVI. Hemodynamic testing may be performed before and after a procedure to document objective improvement and predict long-term success.

Patients with CVI require treatment for limb swelling, skin changes, and ulceration, as well as the pain and disability associated with these objective signs. Although cosmetic considerations should not be ignored, the primary concern in CEAP classes 3–6 is to effectively obliterate abnormal reflux and minimize recurrence for long-term symptom resolution.

In this chapter, diagnostic evaluation and indications for intervention in these patients will be discussed. The options for surgical management of various anatomic types of venous insufficiency will be reviewed and contrasted to nonsurgical techniques.

PRESENTATION OF PATIENTS WITH CVI

A commonly held perception is that less severe CVI (CEAP clinical classes 2–3) is typically a sequela of superficial venous reflux, whereas more severe CVI (CEAP classes 4–6) is associated with deep venous reflux. For this reason, the majority of patients treated with venous leg ulcers are never referred to a venous specialist for consideration of a corrective procedure. It is mistakenly believed that all are due to deep venous disease and that none are candidates for correction of reflux or obstruction. Several authors have defined the anatomy of reflux in patients with advanced CVI, and isolated saphenous or saphenous and perforator reflux is not uncommon, occurring in 20 to 35% of patients in various series. Also, as outlined by Drs. Neglen, Raju, and Kistner in other chapters, many patients with deep venous insufficiency causing severe CVI may be improved with surgical or endovenous procedures, reducing symptoms and the incidence of recurrent ulcers.

For these reasons, all patients with advanced CVI with or without limb ulceration who are candidates for corrective procedures should be studied with diagnostic studies to determine the anatomy and physiology of their individual case. Referral to a venous specialist familiar with surgical and nonsurgical options will allow the optimal method of correction to be selected.

DIAGNOSTIC TESTING FOR PATIENTS WITH CVI

The rational treatment of patients with chronic venous insufficiency (CVI) and its sequelae requires the use of

noninvasive studies to determine the anatomic and hemodynamic characteristics of the patient's venous system. The treatment of lower extremity arterial insufficiency (AI) clearly is guided by the use of ankle/brachial index and Doppler waveform information to define the hemodynamic effect of anatomic lesions, which are clearly illustrated by artieriography. This information, in addition to the history and physical examination, allows the clinician to determine which patients require intervention, and the optimal choice of intervention when needed. In the treatment of CVI, this same information, the anatomic sites of venous dysfunction, and the hemodynamic importance of this dysfunction, are required to allow treatment plans to be formulated and optimal results to be achieved. Selecting surgical therapy without a knowledge of which vein segments are abnormal is essentially blind surgery and cannot result in optimal results.

Duplex Ultrasound

Imaging techniques using ultrasound combined with Doppler interrogation of the venous system have been validated as sensitive methods of diagnosis of deep venous thrombosis. Important information for patients with CVI that would be detected with this technique includes the presence or absence of venous obstruction or other changes typical of previous DVT. This information will help to determine whether the patient's CVI is due to obstruction, reflux, or both (pathophysiology). However, the assessment of reflux is limited to qualitative information. Valsalva maneuvers or manual compression may be performed with the patient supine to look for reflux in the common femoral vein or saphenous vein, but these are not reproducible, quantitative tests of venous reflux. However, the presence of outflow obstruction in the iliac veins and/or IVC often can be detected looking at flow patterns, phasicity, and respiratory variation in the common femoral vein. In addition to an examination of the deep and superficial systems, the perforator veins are carefully examined for evidence of incompetence.

Unfortunately, the accuracy of duplex at identifying incompetent perforator veins is somewhat controversial. Most authors agree that perforating veins demonstrated on duplex to allow flow in the reverse direction with manual augmentation maneuvers, from deep to superficial system, are incompetent. The hemodynamic significance of incompetent perforators is not well established, because most occur along with either deep or superficial reflux, and the contribution of each to venous insufficiency is not usually known. The vascular technician must be experienced in the typical anatomic location of perforators and expert in their imaging to allow a proper evaluation of perforator incompetence.

Second, venous reflux in the deep and superficial venous systems is evaluated with the patient in the standing position using duplex ultrasound and either manual compression or a rapid inflation/deflation system to elicit reflux. The measurement of valve closure times after release of distal compression is described in detail in Chapter 18. In studies of normal volunteers and patients with CVI, a normal valve closure time of <0.5 has been defined. Systematic interrogation of the common femoral, superficial femoral, popliteal, Greater Saphenous, and lesser saphenous veins is conducted, allowing an anatomic map of venous reflux in the limb to be constructed.

Using this information, the clinician can determine the etiology, anatomy, and pathophysiology of CVI for the patient. For example, the patient that has superficial and perforator disease may be differentiated from the patient with superficial and deep reflux, allowing alternate treatment plans to be selected. Although duplex evaluation provides detailed information on the anatomy of venous disease, it cannot define the importance of anatomic abnormalities in the venous function of the limb. Clearly, one patient with gross reflux in the saphenous vein will have no resultant symptoms, whereas another patient may have class 6 CVI with an active ulcer from saphenous reflux alone. The clinical assessment of the severity of CVI is often subjective, so testing that allows objective measurement of the hemodynamic performance of the lower extremity venous system would greatly assist with patient assessment and treatment decisions.

Photoplethysmography

Plethysmography is defined as the determination of changes in volume, and various techniques of plethysmography have been evaluated in the noninvasive examination of the venous system. Photoplethysmography (PPG) utilizes a transducer that emits infrared light from a light emitting diode into the dermis. The backscattered light is measured by an adjacent photodetector and displayed as a line tracing. The amount of backscattered light varies with the capillary red blood cell volume in the dermis. Using this technology and provocative limb maneuvers, an assessment of the venous system is obtained. A representative PPG tracing is reproduced in Figure 55.1 and illustrates the primary measure obtained, the refill or recovery time (VRT), which represents the time required for the PPG tracing to return to 90% of baseline after cessation of calf contraction. PPG does not produce a quantitative measure, but the refill time has been found to correlate closely with ambulatory venous pressure (AVP) measurements. The use of an above knee tourniquet inflated to 50 mm Hg has been described to differentiate the contribution of the deep and superficial venous systems to venous reflux.

Limbs affected with CVI typically have a much shorter VRT than normal limbs. As such, PPG can provide a relatively simple measure of whether venous insufficiency is

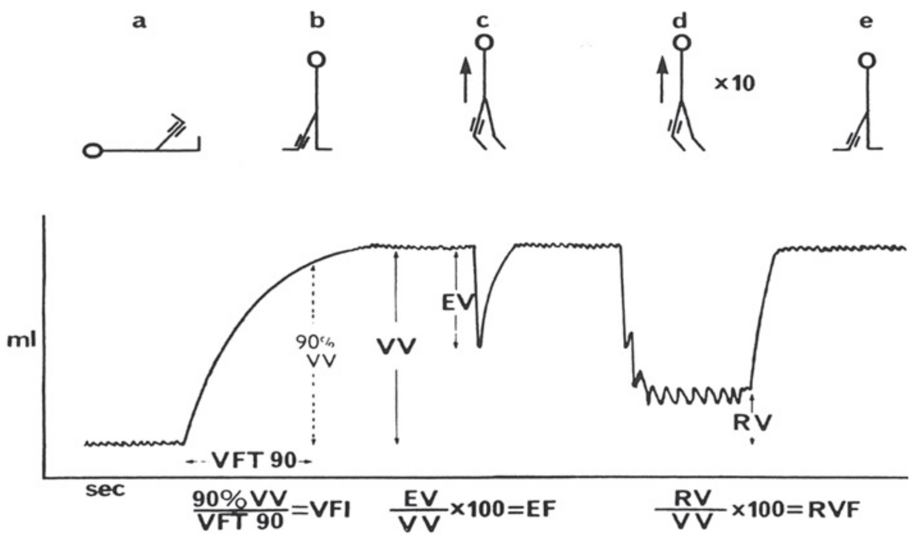

FIGURE 55.1 Diagrammatic representation of hemodynamic values obtained from air plethysmography. VV = venous volume, VFI = venous filling index, EF = ejection fraction, RVF = residual volume fraction. Reprinted with permission from Cristopoulos et al, J Vasc Surg. 1987, 5:148–159.

present or not. However, the technique can vary depending on the site of photosensor placement and the small sample area obtained. Placement near the site of a varicose vein or perforating vein may affect results, and patient compliance with the maneuvers required can be problematic.

PPG measurements have not been proven to be a strong discriminator of the severity of CVI. Nicolaides and Miles reported that normal limbs were well identified by a PPG refill time of greater than 18 seconds with their protocol. Abnormal limbs with CVI consistently had a refill time of <18 seconds. However, in the abnormal group, PPG refill time could not differentiate between degrees of CVI, with similar PPG refill times obtained in patients with AVP measurements ranging from 45 to 100 mm Hg. Therefore, PPG is a poor test for assessing the results of venous corrective surgical procedures.

In summary, PPG is a reasonable measure of the presence or absence of CVI that is best used when no further information concerning the venous hemodynamic situation is desired. However, if information concerning the severity of CVI, or an evaluation of the improvement after venous surgery is required, a quantitative test will be more useful.

Air Plethysmography

Air plethysmography (APG) utilizes a technique to improve on the shortcomings of PPG and other types of plethysmography that have limited sampling areas. It employs a low-pressure air-filled cuff measuring 30 to 40 cm in length that is applied to the lower leg, allowing quantitative evaluation of volume changes of the entire lower leg from knee to ankle. The technique is fully described in Chapter 5. Briefly, the patient lies supine initially with the leg elevated and supported at the heel allowing the cuff to be applied to the lower leg. The cuff is inflated to a pressure of 6 mm Hg to provide snug apposition to the limb without compressing the superficial veins. A baseline volume in the supine position is obtained with the patient resting. The patient then moves to a standing position supported by a walker to remove weight from the tested limb. The volume tracing gradually increases until a plateau is reached. The patient then performs one calf contraction/tiptoe maneuver followed by rest. A subsequent series of 10 tiptoe maneuvers completes the test procedure. The test protocol may be repeated with the use of a thigh tourniquet to isolate the deep venous system from the superficial system.

In Figure 55.1 the data calculated from the tracings obtained are illustrated. The venous volume (VV) is the difference in limb volumes obtained in the resting and standing positions. The venous filling index (VFI) is calculated by measuring 90% of the VV and dividing this volume by the time the limb requires to refill to 90% of the VV after moving to the standing position. Expressed in cc per second, VFI measures the average filling rate of the dependent leg and is slow in normal limbs. The volume of blood ejected with one tiptoe movement divided by the VV gives the ejection fraction (EF), and the limb volume remaining after 10 tiptoe movements divided by the VV gives the residual volume fraction (RVF).

In 1988, Christopoulos et al. described the use of APG for evaluation of normal limbs and those affected with CVI. A VFI <2 ml/second was associated with clinically normal limbs, and increasing levels of VFI were associated with more severe symptoms (see Table 55.1).[1] The VFI is believed

TABLE 55.1 Prevalence of the Sequelae of Venous Disease in Relation to VFI in 134 Limbs with Venous Disease Studied with Air-Plethysmography

VFI, ml/sec	Swelling(%)	Skin Changes(%)	Ulceration (%)
<3	0	0	0
3–5	12	19	0
5–10	46	61	46
>10	76	76	58

From Reference 1.

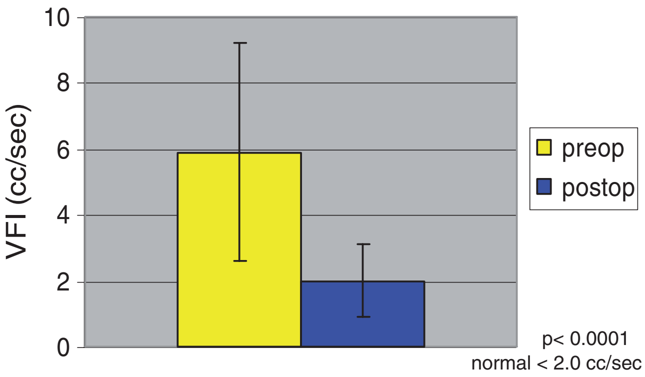

FIGURE 55.2 Median venous filling index (VFI) values measured before and after superficial venous ablation, with no specific treatment of incompetent perforator veins. Normal VFI is <2 ml/sec.

to provide a reasonable approximation of the global function of the lower extremity venous system in resisting reflux in the standing position.

The EF and RVF are measures of the efficacy of the calf muscle to pump blood out of the leg. The RVF was found to correlate closely with AVP throughout the range of AVP measurements, with lower RVF values representing better calf pump function (normal RVF defined as <35%).

In an evaluation of 186 limbs, Criado et al. assessed the ability of APG parameters to predict the clinical severity of CVI. This is important primarily in the objective use of these tests for selection of patients for venous surgery and the monitoring of results and improvement after surgery. They reported that, of the APG parameters measured, VFI was the best predictor of the clinical severity of CVI. Ninety-three percent of limbs with a VFI <2 ml/sec were clinically class 0 and only 9% of patients with a VFI >5 were Class 0. VFI was found to have an 80% sensitivity and 99% positive predictive value for detecting abnormal reflux.[2] Unfortunately, using their methodology, the use of a thigh tourniquet was unreliable in predicting the presence or absence of superficial versus deep venous disease. EF measurements were unable to differentiate between classes of CVI, and RVF measurements, though able to differentiate, were less useful than the VFI.

Further work with APG measurements has demonstrated that the postoperative VFI can predict the long-term symptomatic outcome for patients after venous surgical procedures. Ninety-four percent of patients in whom the VFI corrected to <2 ml/sec after surgery were asymptomatic at a mean follow-up time of 44 months (see Figure 55.2).[3]

In summary, APG, by sampling a large portion of the calf area, provides a better measure than PPG of the global venous function of the limb. It provides a quantitative analysis that appears to be useful in the selection and follow-up of patients undergoing venous reconstructive or ablative surgery.

INDICATIONS FOR INTERVENTION

The indications for intervention in patients with CVI are variable and depend on the severity of symptoms, options for correction, and the functional and medical status of the patient. Patients in CEAP clinical class 3 and 4 suffering symptoms of swelling and skin changes may be managed with compression stockings and skin lubricants with general improvement. However, compliance with compression stocking use generally is believed to be poor in the long term. Patients who are candidates for a corrective procedure typically will choose intervention, particularly younger, more active patients. In clinical classes 5 and 6, the primary indication for intervention is to reduce the risk of recurrent ulceration. Patients with active ulcers can expect ulcer healing in 10 to 12 weeks on average using various high compression bandaging systems.[4] Unfortunately, patients with larger ulcers and those of long duration heal more slowly in most cases. It is not clear whether intervention with correction of CVI will accelerate healing in these cases, but it is reasonable to perform corrective procedures if possible prior to ulcer healing.

Many insurance carriers require a three- to six-month waiting period using conservative therapy for symptomatic CVI prior to approving surgical or endovenous intervention. There are some patients who may be adequately treated with these measures if they are poor candidates for intervention. Given the difficulty in complying with a recommendation for lifelong use of compression stockings, there appears to be little justification to delay intervention in patients with confirmed hemodynamic CVI who are active and good candidates for relatively low-risk venous corrective procedures.

Anatomically, any combination of superficial, perforator, and/or deep venous disease may result in severe CVI. Marston et al. reported that 29% of limbs with CVI and leg ulceration displayed superficial or superficial and perforator disease on standing reflux examination (see Table 55.2).[4] Small saphenous reflux may also be sufficient to cause leg ulceration with no other abnormalities, typically resulting in ulceration near the lateral malleolus. The contribution of incompetent perforators to global venous insufficiency

TABLE 55.2 Anatomic Distribution of Venous Reflux in 178 Limbs with CEAP Clinical Class 6 CVI

Anatomic site	Incidence
Deep alone	43.5%
Deep and superficial	21.0%
Deep, perforator, and superficial	6.5%
Superficial alone	18.1%
Superficial and perforator	10.9%

remains controversial and will be discussed in detail later, but it is clear that some leg ulcers are associated with large incompetent perforators that should be ligated.

A significant percentage of patients with severe CVI are found to have abnormal venous function in multiple systems. Over 27% percent displayed both deep and superficial reflux in a study of 178 limbs with leg ulceration (see Table 55.2). It is not always clear whether these patients will experience an improvement in the severity of symptoms if their superficial or superficial and perforator abnormalities are corrected. This issue will be discussed in detail later.

Hemodynamic evaluation using APG is very useful in the management of patients with multisystem venous insufficiency. Patients with deep and superficial reflux may be treated initially with superficial stripping or ablation and the APG can be repeated to determine the degree of improvement without addressing the deep venous reflux. As noted earlier, post-operative normalization of the VFI is associated with minimal symptoms at late follow-up. Therefore, a patient who has improvement in the VFI with correction of only one anatomic component of their venous reflux can be followed conservatively, whereas a patient with a persistent hemodynamic abnormality with a poor VFI can be considered for further intervention. Ulcer recurrence can also be predicted based on the VFI. McDaniel et al. reported that a post-intervention VFI >4 was associated with a significantly increased incidence of recurrent limb ulceration. Therefore, patients with venous leg ulcers who are treated conservatively resulting in healing may be considered for intervention to correct venous insufficiency based on the risk of recurrence predicted by APG evaluation.

CONVENTIONAL SURGICAL PROCEDURES FOR CORRECTION OF CVI

Superficial Venous Reflux—Great Saphenous Vein

Traditional surgical techniques for removal of the Great Saphenous vein typically have employed ligation of the vein at the saphenofemoral junction and removal of the vein between the groin and knee or groin and ankle using a stripping technique. The goal of high ligation is to identify and divide all venous branches communicating with the saphenofemoral junction (SFJ) to minimize the potential for recurrent reflux pathways resulting in recurrent symptoms. Bergan and others consistently have advocated wide exposure of venous tributaries to their branch points during high ligation. Unfortunately it appears that many patients developing recurrent venous insufficiency do so because of neovascular generation of new venous communications reestablishing the saphenofemoral junction, or dilation of preexisting venous tributaries. At this point it is theorized that the surgical procedure itself is the primary stimulus for neovascularization and there is hope that endovenous techniques may prove to be associated with a lower incidence of recurrent venous insufficiency after intervention. If surgical treatment is chosen, it remains prudent to perform a complete branch ligation as previously described.

Numerous methods have been described for removal of the saphenous veins after high ligation. The current trend is toward minimizing the invasiveness of surgical intervention, and numerous alternatives to surgical stripping have been introduced. However, it should be noted that stripping procedures themselves have undergone a significant evolution. Using minimal incisions, tumescent local anesthesia, ultrasound guidance, and careful dissection, the GSV can be removed through two small incisions with relatively little bruising or postoperative discomfort in the majority of cases. In Chapter 25, saphenous stripping techniques are reviewed in detail. Key advances have included the use of detailed preoperative venous mapping to plan surgery and the use of intraoperative ultrasound to locate the saphenofemoral junction and precisely place incisions. In the absence of significant obesity, the SFJ ligation can be performed through a 2- to 3-cm modified transverse incision. Using ultrasound guidance, the GSV can be located just below the knee and encircled through an incision no larger than 1 cm. We typically use tumescent anesthesia and temporary packing along the saphenous tract to minimize bruising. Patients walk upon leaving the ambulatory surgery center and routinely return to work and other routine activities within several days. In many patients the more significant morbidity comes from the associated stab or powered phlebectomies performed concurrent to saphenous stripping to remove prominent varicosities.

The following issues in superficial venous surgery will be discussed in detail next:

- Saphenofemoral ligation alone or ligation and saphenous stripping
- Saphenous stripping to the ankle or to the knee
- Small saphenous reflux
- Need for concomitant varicosity ablation
- Concurrent deep and superficial insufficiency

Saphenofemoral Ligation Alone or Ligation and Saphenous Stripping

It has long been debated whether high ligation alone or with varicosity ablation is sufficient for the treatment of superficial venous reflux. Proponents argue that preservation of the saphenous vein is preferable to allow later use as a conduit and that the rate of recurrent symptoms without stripping is acceptable. Hammarsten et al. reported a random allocation of 42 patients to high ligation with varicosity avulsion or high ligation with saphenous stripping and varicosity avulsion.[5] In both groups incompetent perforators were ligated whenever present. At a mean follow-up of 52 months there was no difference in the rate of recurrent symptomatic VV between the two treatment groups (12% in those with stripping and 11% in those without). Venous Doppler evaluation of the residual saphenous vein revealed that 78% would be suitable for use as an arterial conduit. Other authors have supported the preservation of the saphenous vein with the majority of veins remaining suitable for use as a vascular prosthesis. However, the frequency with which the saphenous vein will be required for future use is unclear, given the preferential use of an arterial conduit for cardiac revascularization (internal mammary, radial arteries), and the increased use of endovascular techniques for infrainguinal revascularization.

Proponents of high ligation with GSV stripping have noted the increased incidence of recurrent reflux in the saphenous vein after high ligation alone and maintain that optimal results require routine saphenous stripping. Investigators looking at the residual GSV after high ligation without stripping have identified frequent residual reflux in the GSV. McMullin et al. reported residual reflux in 24 of 52 cases (46%) after SFJ ligation and found that those with persistent reflux did not correct venous refilling times measured by PPG.[6] de Haan et al. measured reflux duration and velocities at several levels in the GSV before and after high ligation in 29 limbs.[7] Though nearly all (97%) had reflux in the proximal saphenous vein abolished, 52% demonstrated persistent saphenous reflux at the knee.

The Gloucestershire Vascular Group reported five-year follow-up of 110 limbs randomized to high ligation alone compared to ligation plus stripping.[8] Although patient satisfaction was similar in the two groups, significantly fewer patients in the stripping group required reoperation for recurrent saphenous reflux with symptomatic varicosities (6%) compared to the high ligation only group (20.8%). Regardless of the type of intervention, VV recurrence appears to depend on the length of follow-up. Studies following patients longer than 10 years report that many patients develop recurrent varicosities of some severity. In Fischer's definitive report of the long-term follow-up of limbs treated with high ligation and stripping, 47% of patients followed for an average of 34 years developed clinically evident varicosity recurrence.[9] Although early recurrence was less frequent in some studies in limbs treated with stripping, this benefit is probably lost over time. The primary benefit of stripping appears to be a reduction in the number of limbs requiring reoperation. It has been suggested that this relates to the improved hemodynamic outcome in limbs treated with stripping, resulting in a lower incidence of persistent pain and swelling that would require reoperation.

Balancing the improved hemodynamic result with saphenous stripping has been the occurrence of increased complications with this procedure. Although there is an increased incidence of bruising and hematoma in the thigh with stripping, this can be minimized by the use of tumescent anesthesia and other techniques as noted earlier. The most significant complication attributed to saphenous stripping involves injury to the saphenous nerve. Fully described later, there is a significant incidence of saphenous nerve deficit after stripping that is reduced when stripping stops at the level of the knee. Overall, few patients appear to have long-term deficits from this injury.

In summary, high ligation and varicosity ablation is likely to be an acceptable procedure for less severe classes of CVI where the reduced recovery time and reduced potential for bruising and nerve injuries is more important. Although some patients develop recurrent reflux, several authors have reported that sequential sclerotherapy of saphenous branches is able to eliminate recurrent reflux when it develops.

However, in more severe classes of CVI, the primary aim is to correct the hemodynamic abnormality resulting in symptoms. For many patients, the need for repeat procedures to maintain control of saphenous reflux is undesirable. The high incidence of residual saphenous reflux and significant frequency of reoperation when stripping is not performed argue in favor of high ligation and stripping as the preferred surgical operation for CVI with symptoms due to GSV reflux.

Saphenous Stripping to the Ankle or Knee

If GSV stripping is chosen as a component of a procedure for the treatment of CVI, the surgeon must determine the length of vein to remove. In most cases, the vein refluxes at both the saphenofemoral junction and throughout its course. Traditionally, many surgeons have elected to strip the entire vein from groin to ankle. The saphenous vein is easily identified at the ankle and retrograde passage of the stripper generally is unobstructed. However, the saphenous nerve is in close proximity to the vein beginning just below the knee in many patients and may be susceptible to injury during stripping procedures. For these reasons, some surgeons have recommended limiting stripping at a point just below the knee.

To determine whether a limited GSV stripping to the knee would be sufficient to yield improvement in venous hemodynamics, Nishibe et al. studied 110 limbs before and

after removal of the above-knee segment of GSV using duplex ultrasound APG.[10] They found that venous hemodynamics as measured by APG were markedly improved after limited GSV stripping. The majority of patients experienced correction of the abnormal preoperative VFI (4.0 ± 0.35 ml/sec) to the normal range (1.4 ± 0.15, $p < 0.001$). The incidence of apparent saphenous nerve injury on assessment at two to three weeks after surgery was 4.5%, with most of these patients reporting numbness, mild to moderate pain, or sensitivity to touch in the affected areas.

Holme and colleagues conducted a prospective randomized study in which 163 patients were randomized to high ligation and stripping of the GSV to the ankle (Group A) compared to high ligation and stripping to the knee (Group B).[11] Three months after surgery, 94% of patients in Group A reported good or excellent relief of symptoms compared to 97% of patients in Group B (p = NS). Evidence of saphenous injury was identified in 39% of limbs in Group A compared to 7% in Group B ($p < 0.001$). In a subsequent report, the same authors reported long-term follow-up of the same patient cohort. Three years after randomization, 29% of limbs in Group A were reported to display symptoms of permanent saphenous nerve injury compared to only 5% in Group B ($p < 0.01$). At five years of follow-up, recurrent varices were seen in 10% of patients in each group.

In a detailed study of the incidence and clinical impact of saphenous nerve injury, Morrison and Dalsing evaluated 127 limbs treated with saphenous stripping to the ankle at a mean follow-up of 4.5 years.[12] Overall, 40% of patients reported symptoms of saphenous nerve injury at some point after operation. At last follow-up 17% reported the symptoms were persistent, but only 2.3% reported that the symptoms negatively affected their quality of life.

Although the symptoms of saphenous nerve injury may rarely be severe, minor complaints are frequent. It appears that the hemodynamic results of stripping to the knee are similar to total saphenous stripping in most cases. Therefore, most authors have recommended stripping to the knee as the treatment of choice for axial GSV reflux.

More limited stripping procedures may be considered in patients who demonstrate reflux in the proximal GSV down to a mid-thigh branch and competence below. Another common variation is the GSV demonstrating competence at the saphenofemoral junction but reflux at the knee. Little data is available reporting on results in this group of patients. This pattern of reflux likely occurs due to an incompetent thigh perforator or perforators bringing an increased volume of flow into the GSV such that the resultant pressure in the saphenous causes distal valvular dysfunction at the knee level. Treatment of this pattern of reflux depends on accurate identification of the source of reflux and correction, either by addressing the perforator(s) or stripping the saphenous vein to include the segment containing the reentry reflux source.

Small Saphenous Reflux

Often overlooked is the possibility that severe CVI may be due solely to reflux in the SSV. Labropolous et al. studied 226 limbs with reflux isolated to the SSV, comprising approximately 10% of their patients with CVI.[13] Symptoms were present in 61% of patients, but only 18.5% were severe enough to be classified as CEAP clinical class 4–6. In a report of 20 limbs with isolated lateral perimalleolar ulcers, Bass and colleagues found isolated SSV reflux at the saphenopopliteal junction in 15 (75%).[14] After SSV ligation at the junction, all ulcers healed within 12 weeks. Lin et al. found that SSV incompetence frequently was associated with severe CVI and is less commonly corrected surgically than GSV insufficiency.[15] They recommended that SSV examination and correction should assume greater importance in the management of symptomatic CVI. In general, SSVs with sufficient reflux to cause severe CVI are large, dilated veins with numerous varicose tributaries. Hemodynamic evaluation with plethysmography is often useful to determine whether isolated SSV reflux is hemodynamically significant. Patients with SSV reflux are unlikely to have significant symptoms without an abnormal venous filling index.

Prior to intervention for patients with SSV incompetence, the anatomy of the vein must carefully be determined. The variable course of the SSV has been well documented, and the vein may terminate at numerous points into the popliteal vein, the femoral vein, the vein of Giacomini, or elsewhere. The presence of a large persistent superficial vein in the lateral thigh that does not join the deep system should alert the clinician to the possibility of a variant of Klippel-Trenaunay syndrome with hypoplastic deep veins.

Preoperative mapping of the SSV with ultrasound will assist with operative planning, and marking of the saphenopopliteal junction (SPJ) is frequently useful. However, surgeons performing SPJ ligation frequently are increasingly using intraoperative ultrasound to guide surgical decision-making. The SSV may give off several branches just distal to the SPJ and it is believed to be beneficial to ligate these branches to minimize residual collateral reflux. Similar to GSV surgery, controversy has existed concerning the need for stripping of a portion of the SSV. Although no randomized trials have compared sahpenopoliteal ligation to ligation with SSV stripping, most authors have recommended stripping a portion of the SSV. Stripping generally should not involve the lower third of the calf given the increased risk of injury to the sural nerve. The technique of SSV stripping is described fully in Chapter 32.

Need for Concomitant Varicosity Ablation

Correction of saphenous and perforator insufficiency will improve hemodynamics with reliable reduction in symptom severity. However, to many patients, the primary sign of

their "vein problem" is the visible varicosities, and most prefer varicosity removal or ablation whenever necessary. In conventional surgical treatment, this typically has been performed at the time of saphenous stripping, taking advantage of the anesthetic and eliminating the need for subsequent procedures. Some practitioners prefer to perform saphenous stripping alone, noting that many varicosities will improve after this procedure, never requiring removal. Since the introduction of endovenous ablative techniques, more patients are treated initially with endovenous ablation without varicosity ablation. In many limbs, residual varicosities contract and fade in the absence of continued venous hypertension so that no further ablative procedures are required. Ambulatory phlebectomy or sclerotherapy may be performed after endovenous ablation for limbs with residual varicosities as needed at the patient's request.

Patients with more severe CVI typically have large varicosities that may be less likely to resolve without removal. The author's practice has been to recommend elimination of these varicosities at the time of saphenous correction. If IPVs are present in the calf, they typically communicate with the posterior arch vein rather than the GSV. Varicosity ablation may be important to eliminate outflow pathways for IPVs as described later. Patients with hypercoagulable states are probably at higher risk for thrombosis in residual varicosities, arguing for removal if surgical therapy is chosen for saphenous reflux. However, there is little evidence that hemodynamic or symptomatic improvement depends on varicosity removal in most patients, so this decision must be individualized based on the status of the varicosities and the patient's wishes.

A variety of techniques have been described to address prominent varicosities. The standard technique for surgical removal has involved surgical incisions overlying prominent varicosities and avulsion, followed by limb compression to minimize bleeding and hematoma formation. Over the years, this procedure has been performed through smaller and smaller incisions to its current technique using fine instruments specifically designed to fish out varicosities through micro-incisions (see Figure 55.3). Cosmetic results have improved markedly using this technique, which is described fully in Chapter 27. It generally is recommended that varicosity ablation be performed prior to stripping because stripping results in distal venous hypertension increasing the potential for severe bruising and hematoma formation if ablation is performed after stripping.

Although varicosities can be ablated reliably with this technique, it is a tedious, time-consuming method, particularly in patients with extensive varicosities. For this reason, Spitz developed an alternative method for varicosity removal utilizing a powered phlebectomy device allowing large areas of varicose veins to be removed rapidly through two small incisions (Trivex, Smith, and Nephew, Inc, Andover MA). The technique is fully described in Chapter 28. In a randomized study, the results of powered phlebectomy were compared to surgical varicosity removal. Powered phlebectomy was found to significantly reduce the number of required incisions and a trend toward shorter operative time was noted. No difference was found in the incidence of bruising, cellulites, pain, or recovery time. Cosmetic results were perceived by the patients to be equivalent and no difference in varicosity recurrence was found six and 12 months after surgery. The authors concluded that the results of powered phlebectomy were equal to standard phlebectomy, with the potential to shorten surgical time particularly in patients with more extensive varicosities.

FIGURE 55.3 Stab phlebectomy using mini-incisions to allow removal of extensive varicosities with improved cosmetic result.

Residual varicosities may also be treated with sclerotherapy using a variety of sclerosants. Liquid sclerosants have been somewhat limited in most clinicians' hands by varicosity size, but foam sclerosants appear to allow larger varicosities to be treated successfully in many cases.

Results of Conventional Saphenous Surgery

Numerous studies have reported on short- and long-term results after saphenous surgery, including symptom relief, varicosity resolution, recurrent varicosities, need for reoperation, and quality of life improvement. Bergan reported on the results of 702 limbs undergoing conventional surgical procedures in an outpatient setting.[16] The most common complication was ecchymosis in the medial thigh, none severe enough to require further treatment. Less frequent complications included numbness in the saphenous nerve distribution (6.5%) and lymphocele along the saphenous tract (2.5%). There were no reported cases of deep vein thrombosis (DVT) in this series. Hospitalization was required in only three patients.

The hemodynamic improvement in patients undergoing saphenous surgery has been well documented. Using APG, correction of saphenous reflux has been demonstrated to

result in marked improvement in venous filling index, ejection fraction, and residual volume fraction.[3] Patient satisfaction with the procedure is generally high, but not universally so. Mackay et al. reported on 155 patients who were treated with high ligation and GSV stripping assessed by a questionnaire.[17] Nearly two-thirds of patients reported a perceived post-operative complication within the first two weeks after surgery, most relating to bruising, pain, and numbness. Six months after surgery, 80% of patients were satisfied with the outcome, with the most common reason for dissatisfaction being residual varicosities.

Chronic venous disease has been reported to negatively affect patient quality of life as assessed by a variety of outcome measures. Using various methodologies, investigators have reported that saphenous vein surgery significantly improves quality of life both initially following surgery, and at mid-term follow-up several years later.

For patients with CEAP clinical class 5 and 6 disease, Barwell et al. performed a randomized study comparing the efficacy of saphenous stripping plus compression compared to compression alone for healing and prevention of venous leg ulcers.[18] Termed the ESCHAR study, 500 patients with isolated superficial reflux (60%) or combined superficial and deep venous disease (40%) were enrolled. Demographic factors were similar in the two groups. Ulcer healing was no different with 65% healed in each group by life table analysis at 24 weeks after randomization. In the group with healed ulcers, mean follow-up time was 14 months. Significantly fewer patients in the surgery group experienced recurrent ulceration (15%) compared to the compression alone group (34%). Adverse events were infrequent (<5% in each group) primarily comprised of compression bandage injuries in the conservative group and wound infection (n = 5) in the surgical group.

In summary, saphenous stripping procedures have a proven ability to correct venous hemodynamic dysfunction due to abnormal reflux resulting in reduced patient symptoms and improved quality of life in the majority of patients. Though not able to speed healing for venous leg ulcers, the rate of recurrent ulceration is reduced significantly compared to treatment without surgical correction. Complications of surgery are most often minor and self-limited, but an occasional patient may develop nagging discomfort from saphenous neuralgia, and a rare possibility of DVT cannot be ignored.

Alternatives to Conventional Saphenous Surgery

Numerous alternatives to conventional saphenous surgery have been promoted to effectively eliminate saphenous reflux without the need for surgical incisions or saphenous removal. These include:

- Hemodynamic correction of varicose veins (CHIVA)
- External banding to restore saphenous competence
- Endovenous ablation
  - Radiofrequency
  - Laser
- Sclerotherapy
  - Ultrasound-guided
  - Foam

When considering the optimal management of patients with more severe CVI, the primary goal is to abolish axial reflux and prevent its recurrence. In these patients, recanalization or reopening of the previously treated saphenous vein usually results in recurrence of the preintervention symptoms, including pain, swelling, worsening skin changes, and possibly ulceration. Most patients who have suffered leg ulcers related to CVI, if given a choice, will choose an intervention that is most likely to minimize the risk of ulcer recurrence. None of the alternatives to saphenous stripping have been studied in a randomized trial to prove benefit in reducing venous ulcer recurrence. As a surrogate we can assume that if the GSV or SSV remains closed with no reflux throughout the length from groin to knee, the patient should experience a benefit similar to high ligation and stripping procedures.

Saphenous banding procedures to attempt to reestablish competence of the sentinel valve at the SFJ using either external banding materials, or endovenous radiofrequency have met with variable results. Despite encouraging reports of success in some studies, others have generated disappointing results with high recurrence rates, such that these techniques are not widely used currently.

Sclerotherapy using ultrasound guidance has been described as a means for occluding the GSV or SSV, thereby correcting reflux. Initial attempts employed liquid sclerosants, and though many saphenous veins were treated successfully, recanalization rates were high in many studies (18.8–23.8%). More recently, foam sclerotherapy has been studied for occlusion of the GSV, with several studies finding improved results compared to liquid sclerotherapy.[19] In a randomized study, 88 patients were treated with either sclerosing foam or sclerosing liquid via direct puncture of the GSV under duplex guidance.[19] Three weeks after treatment repeat examination with duplex ultrasound revealed that only 40% of patients treated in the liquid sclerotherapy group had eliminated reflux throughout the GSV compared to 84% in the foam sclerotherapy group. From these studies, it appears that the recurrence rate for liquid sclerotherapy is unacceptably high for treatment of the GSV. Using a foam sclerosant will significantly increase success rates, but they may still be inferior to high ligation and stripping. Randomized studies including quality of life evaluations would further determine whether sclerotherapy has a role in the treatment of saphenous reflux.

Of the listed alternatives to saphenous ligation and stripping procedures, endovenous ablation has been the most widely studied, including randomized comparisons to stripping. The goal of radiofrequency (RFA) or laser ablation (EVLA) is to ablate the saphenous vein percutaneously eliminating saphenous reflux, thereby producing the same hemodynamic benefit as high ligation and saphenous stripping with no incisions, fewer complications, and faster recovery to full activity. Early studies with both techniques have demonstrated initial saphenous closure rates of over 90%. Long-term data reporting the incidence of saphenous recanalization are now emerging, with acceptable three to five year results. In the EVOLVeS study, RFA was compared to ligation and stripping in 86 limbs, including quality of life measures and follow-up ultrasound examinations at routine intervals. Initial success rates at elimination of saphenous reflux were 100% in the stripping group and 95% in the RFA group.[20] Time to return to normal activities and return to work were significantly less in the RFA group. Quality of life surveys revealed a significantly better global score and a significantly better pain score for RFA one week post-procedure, but these differences progressively decreased over time. At two years of follow-up, two patients in the RFA group had developed recanalization of an initially closed saphenous vein (4%), but global quality of life scores still favored RFA. One patient in the RFA group and four treated with ligation and stripping were found to have evidence of neovascularization on ultrasound examination. Recurrent VV occurred in 14% of RFA limbs and 21% of stripped limbs (p = NS).

Clearly, further study in larger patient groups is required to define the optimal use of endovenous procedures. However, in amenable patients, these techniques appear to be viable alternatives to surgical stripping. Long-term recurrence rates must be carefully studied, but the possibility that endovenous ablation will produce less neovascular regeneration at the SFJ is intriguing and will certainly be followed closely.

Combined Deep and Superficial Venous Insufficiency

Treatment of patients with symptomatic CVI and isolated superficial venous insufficiency usually is recommended given the reproducible improvement with correction of saphenous reflux and the low-risk procedures available for this patient group. In patients with CEAP class 4–6 disease, superficial insufficiency often is identified in combination with deep disease. As noted earlier, 27% of limbs studied with active or healed ulcers were reported as having combined reflux. In this situation the clinician must determine whether symptom improvement is likely from treatment of superficial reflux alone, or if the patient is more likely to require deep venous reconstruction.

Several authors have reported that when superficial reflux in the GSV or SSV is present, the more proximal deep vein segment occasionally will reflux solely due to the superficial vein incompetence. Correction of the superficial reflux reliably results in resolution of the deep vein segment reflux. In this situation GSV incompetence would be seen along with reflux in the common femoral vein, but the femoral and popliteal veins would be competent. With SSV reflux, popliteal reflux would be noted cranial to the SPJ, but not caudal to the junction. With these patterns of reflux, superficial ablative procedures are recommended using the same criteria used for superficial incompetence alone.

Treatment of limbs demonstrating true deep venous insufficiency, defined as reflux in the femoral and popliteal veins, combined with superficial reflux is controversial. Walsh and Sales reported resolution of deep venous reflux after GSV stripping in over 90% of cases, but Scriven reported that deep venous reflux usually did not correct. Puggioni et al. recently reported a study of 38 limbs with combined deep and superficial reflux studied with duplex US before and after saphenous stripping.[21] Deep venous reflux was corrected in one-third of patients, and femoral vein reflux corrected more frequently when only segmental reflux was present in that vein rather than axial reflux throughout the deep venous system. The authors note that the majority of limbs reported by Walsh and Sales demonstrated segmental reflux that may be more likely to correct with superficial surgery than axial reflux.

Padberg and colleagues reported a hemodynamic follow-up of 11 limbs with deep and superficial disease treated with superficial stripping and perforator ligation in some cases.[22] Although only 27% of limbs studied postoperatively were found to have correction of deep venous reflux, marked hemodynamic improvement was demonstrated. The venous filling index decreased from 12 ml/sec preoperatively to 2.7 ml/sec postoperatively, and clinical symptom scores decreased from 10 to 1.4. This data suggests that, though superficial and perforator surgery in the presence of deep venous incompetence may not correct deep reflux, it usually will result in significant hemodynamic and symptomatic improvement.

In summary, it is reasonable to consider superficial ablative intervention in patients with combined deep and superficial insufficiency. Those with proximal or segmental reflux are more likely to benefit than patients with full axial reflux in the entire deep system. Hemodynamic evaluation with plethysmography before and after saphenous stripping or ablation can determine the degree of improvement and predict long-term symptomatic improvement.

The Significance of Perforator Reflux in CVI

The incidence of perforator incompetence increases as the clinical severity of CVI worsens. The majority of limbs

in CEAP clinical classes 5 and 6 have been reported to contain perforators with incompetence on duplex imaging. For this reason, some clinicians believe that incompetent perforators should be corrected whenever they are diagnosed. Unfortunately it is difficult to clearly determine the hemodynamic significance of incompetent perforators because they usually are seen in limbs that also display superficial and/or deep system incompetence. There clearly are cases where incompetent perforators are seen in a limb previously treated with saphenous stripping with persistent symptoms of CVI. In these patients, perforator interruption is necessary. But it is unclear whether perforators should routinely undergo ligation in severe CVI at the time of saphenous ablation.

Conventional Surgical Ligation of IPVs

When the surgeon believes that IPVs are associated with clinical symptoms, elimination of perforator reflux can be performed using a variety of techniques. Open surgical ligation, mini-incision ligation, subfascial endoscopic ligation, and percutaneous ablation can all be considered. Until the last decade, only open surgical perforator ligation was performed, usually using the Linton procedure. As originally described by Linton, the procedure involves a medial lower limb incision placed over the site of the clinically significant IPVs. Dissection proceeds down to the level of the fascia where the perforators are located and ligated with suture ligatures (see Figure 55.4). The use of skin flaps was advocated to help reduce the potential for skin breakdown at the incision site postoperatively.

Though the Linton procedure was effective at eliminating perforator reflux, it has been associated with a high incidence of complications, mostly occurring at the incision site in the area of hyperpigmented, scarred skin typical of advanced CVI. In a report of 37 limbs treated with the Linton procedure, Stuart et al. reported that calf wound complications occurred in seven patients (19%), and the average hospital time was nine days.[23] Recurrent ulceration was reported in 7 to 22% of treated limbs at varying lengths of follow-up after the Linton procedure.

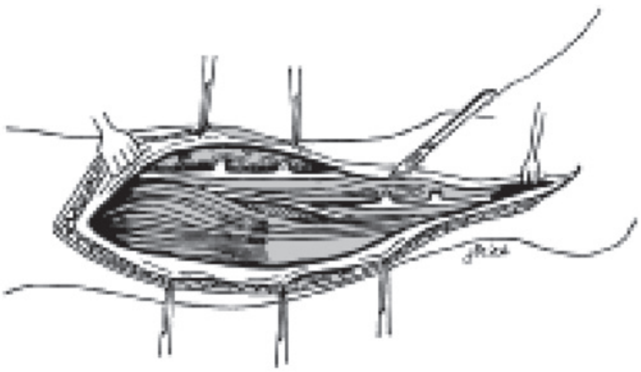

FIGURE 55.4 Incision with flap dissection for Linton procedure.

For these reasons, alternate methods were developed to ligate IPVs while eliminating the need for surgical incisions in the area of poor skin expected to be at risk for compromised wound healing. The most widely performed alternative to the Linton procedure is the use of endoscopy to facilitate subfascial perforator ligation (SEPS) through a remote incision in more healthy tissue just below the knee. See Chapter 56 for a full description of this technique. The primary benefits of this technique have been reported to include more rapid recovery and fewer perioperative complications with equivalent hemodynamic results in comparison to the Linton procedure. In a retrospective comparison of SEPS ($n = 27$) to the Linton procedure ($n = 29$), Sato et al. reported similar rates of ulcer healing and recurrence, as well as a similar improvement in venous dysfunction scores in the two groups. In the Linton group, 45% of patients developed incision-related complications, compared to only 7% in the SEPS group ($p < 0.005$).[24] In a prospective comparison of the Linton procedure to SEPS, Pierik et al. randomized 39 patients to open or endoscopic perforator ligation.[25] In the open group, 53% of patients developed postoperative wound infection compared to 0% in the SEPS group ($p < 0.001$). Ulcer healing rates and recurrence rates were similar in the two groups.

It appears clear that when perforator ligation is deemed necessary, the SEPS procedure is preferred to open surgical ligation. Other alternate options have been reported for treatment of refluxing perforators. Perforator ligation has been reported using a mini-incisional technique minimizing wound complications. Results have been reasonably good but experience is limited. Initial reports of the use of endoluminal techniques have suggested that percutaneous ablation of perforator veins is feasible. Larger prospective studies are needed to determine the efficacy of these less invasive methods.

A more fundamental question concerns the indications for perforator ligation. This remains controversial with proponents arguing that perforators are frequently present in severe CVI and should be ligated whenever present. Skeptics argue that perforators are usually present in combination with superficial and/or deep venous incompetence and the relative contribution of the incompetent perforator to venous insufficiency is less important. Iafrati et al. reported on the treatment of 51 limbs with perforator reflux and leg ulcers using SEPS.[26] Venous disability scores improved significantly after the procedure, and 74% of limb ulcers healed within six months. The recurrent ulceration rate was low at 13%. Excellent results were obtained, but 35 of the 51 limbs were treated concomitantly with saphenous or varicose vein removal. Of note, SEPS performed without saphenous surgery was associated with delayed ulcer healing.

Tawes et al. reported a large retrospective multicenter experience using SEPS in over 800 limbs with CVI.[27] The majority of patients (532) were in CEAP clinical class 5 or 6. Concomitant GSV removal was performed in 55% of cases. Reported results were excellent with 92% of limb ulcers healing at four to 14 weeks after SEPS. Recurrent ulceration occurred in only 4% at a mean follow-up of 15 months. From this review, the authors concluded that until definitive level I evidence is available, SEPS is advocated as optimal therapy for patients with CVI and incompetent perforator veins.

Mendes et al. studied a common subset of patients with IPVs, those with concomitant saphenous reflux and IPVs.[28] Twenty-four limbs were studied before and after surgery with duplex ultrasound and APG. In all limbs, saphenous stripping was performed, with powered phlebectomy added in patients with prominent varicosities. No SEPS or other specific treatment for the IPVs was performed. After surgery, 71% of the limbs no longer contained IPVs. Hemodynamic improvement on APG occurred in all limbs, with the VFI improving from 6.0 ± 2.9 preoperatively to 2.2 ± 1.3 after surgery ($p < 0.001$). They concluded that either the varicosity ablation performed an extrafascial perforator ligation by removing the outflow tract for the IPVs, or the IPVs were of relatively little hemodynamic importance in comparison to saphenous reflux in this patient group.

It is not clear whether IPVs found in limbs coexisting with deep venous reflux should be ligated, particularly in the absence of corrective surgery for the deep venous system. In the North American SEPS Registry report, there was an increased incidence of leg ulcer recurrence in patients with deep venous insufficiency after SEPS. Other authors, including Tawes et al., still recommend SEPS in these patients, believing that venous hypertension will improve after perforator ligation despite the presence of continued deep venous reflux. No prospective randomized studies have been performed to further evaluate these important questions.

It is obvious that the treatment of limbs found to contain IPVs remains controversial in many situations. Perhaps the primary problem in this debate is the lack of a comprehensive definition of perforator incompetence based on their potential to cause venous hemodynamic dysfunction. We currently treat all IPVs similarly, and there is significant variation in the criteria for perforator incompetence in reported studies. This situation would be similar to considering an arterial stenosis of 30% similarly to a 90% stenosis. Delis and colleagues previously suggested that all perforators demonstrating outward flow are not equal, proposing that the volume of outward flow in one second after compression release (based on perforator size and velocity of reflux) may be used to define classes of perforator reflux.[29] They proposed that the early hemodynamic function of the IPV determines its clinical impact on the leg, rather than the duration of reflux. The maximum diameter of IPVs may also be important, such that a 5 mm IPV with a high velocity of reflux would be expected to cause a significantly greater hemodynamic impact than a 3 mm perforator that refluxes in the outward direction, but only at low velocity. Further research on diagnosis and management of IPVs is required to allow optimal treatment of IPVs.

CONCLUSION

In patients with severe CVI, the primary goal is elimination of abnormal venous reflux resulting in venous hypertension. Rational treatment of this diverse group of patients requires detailed anatomic and hemodynamic assessment with duplex and plethysmography. Post-procedure reassessment can reveal the results of therapy and direct further management. Standard surgical techniques for correction of superficial and perforator incompetence are being replaced by less invasive methods that appear in early and mid-term studies to have comparable symptomatic and hemodynamic results. Long-term study will be required to evaluate the critical areas of neovascularization and symptom recurrence after these alternative methods.

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CHAPTER

56

Subfascial Endoscopic Perforator Vein Surgery (SEPS) for Chronic Venous Insufficiency

PETER GLOVICZKI, MANJU KALRA, and ALESSANDRA PUGGIONI

Surgical interruption of incompetent perforating veins was first suggested by Linton in 1938[1] to treat patients with venous ulcers. The rationale for ligating incompetent perforators was to decrease ambulatory venous hypertension in patients with advanced venous disease by decreasing abnormal transmission of pressure from the deep to the superficial veins. Linton's original operation, that required a long skin incision, resulted in a high rate of wound complications. Subsequently proposed operations using shorter skin incisions were either incomplete or, similar to Linton's operation, resulted in frequent wound complications. Subfascial endoscopic perforator vein surgery (SEPS) was developed to replace the open techniques and it became instantly popular because of the minimally invasive nature of the procedure combined with a lesser rate of wound complications. SEPS has been an effective, minimally invasive technique to interrupt incompetent medial perforating veins of the leg.[2–25]

SURGICAL TECHNIQUE

SEPS was first performed in Germany by Hauer in 1985, who used a simple one-port endoscopic instrument to interrupt perforating veins.[2] Two main techniques for SEPS have been developed.

The first has been a perfection of the original technique of Hauer, by Fischer,[3,5,14] with further development by Bergan and colleagues,[9,11,18] Wittens and Pierik.[7,13,20,25] It uses a single scope with channels for both the camera and working instruments (see Figure 56.1). Improvement in instrumentation for this technique resulted in using carbon dioxide insufflation through the single working channel to inflate and enlarge the subfascial space.

The second technique of SEPS uses instrumentation from laparoscopic surgery, and it was introduced by O'Donnell.[23] Carbon dioxide insufflation was added to this technique simultaneously by Conrad in Australia[6] and by our group at the Mayo Clinic.[8,15,21] The two-port technique employs one port for the camera and a separate port for instrumentation, thereby making it easier to work in the subfascial space. The 5 mm port is placed more posterior, halfway between the main port and the ankle. First the limb is exsanguinated with an Esmarque bandage and a thigh tourniquet is inflated to 300 mmHg to provide a bloodless field. A 10-mm endoscopic port next is placed in the medial aspect of the calf 10 cm distal to the tibial tuberosity, proximal to the diseased skin (see Figure 56.2). A balloon dissector is used to widen the subfascial space and facilitate access after port placement. The distal 5-mm port is placed halfway between the first port and the ankle (about 10–12 cm apart), under direct visualization with the camera. Carbon dioxide is insufflated into the subfascial space and pressure is maintained around 30 mmHg to improve visualization and access to the perforators. Using laparoscopic scissors inserted through the second port, the remaining loose connective tissue between the calf muscles and the superficial fascia is sharply divided.

The subfascial space is then explored from the medial border of the tibia to the posterior midline, down to the level of the ankle and up to the level of the 10-mm port. All direct and indirect perforators encountered are occluded and divided with a harmonic scalpel, electrocautery, or the vein is cut with scissors between clips. A paratibial fasciotomy next is made by incising the fascia of the posterior deep compartment, close to the tibia, to avoid injury to the posterior tibial vessels and the tibial nerve. The posterior tibial perforators (Cockett II and Cockett III) are located frequently within an intermuscular septum, or frankly, in the

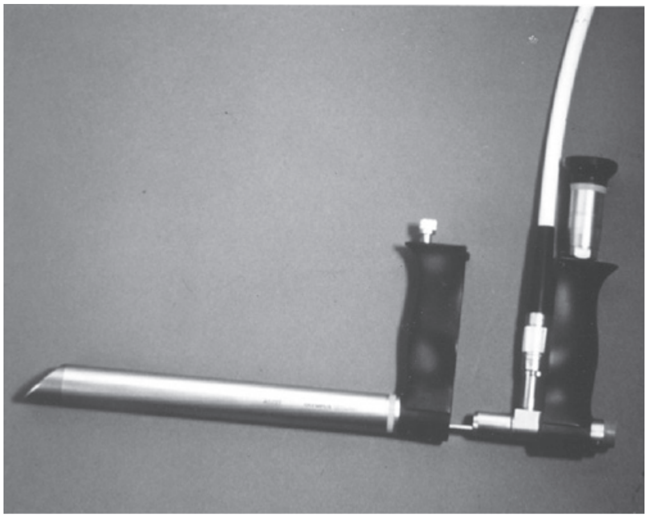

FIGURE 56.1 Olympus endoscope for the subfascial perforating vein interruption. The scope can be used with or without carbon dioxide insufflation. It has an 85-angle field of view, and the outer sheath is either 16 or 22 mm in diameter. The working channel is 6 × 8.5 mm, with a working length of 20 cm.[39]

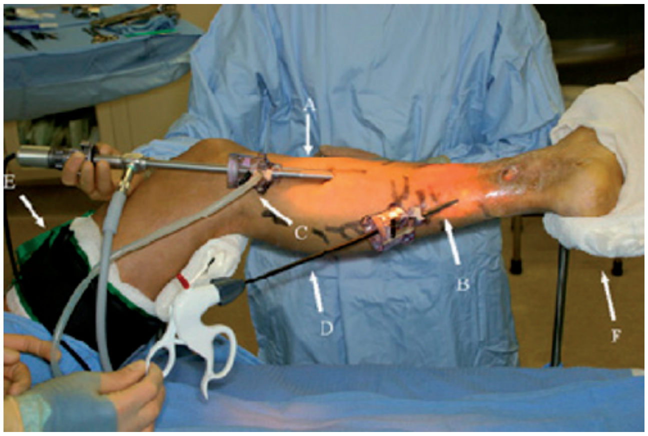

FIGURE 56.2 Two-port technique of SEPS. One 10-mm port (**A**) for the camera and a 5-mm port (**B**) for instrumentation are inserted. Carbon dioxide is insufflated into the subfascial space (**C**) and pressure is maintained around 30 mmHg. All perforators encountered are divided with the harmonic scalpel (**D**). Note the thigh tourniquet (**E**) and the leg holder (**F**) to facilitate the operation.[38]

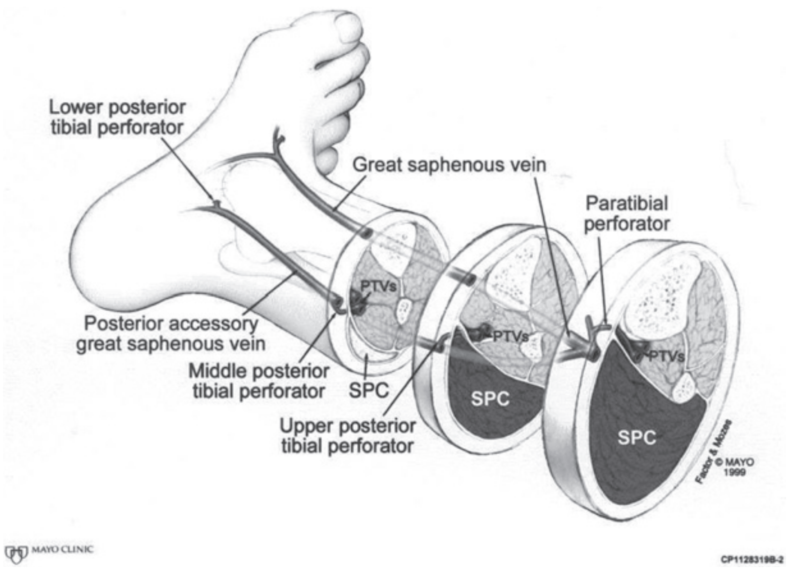

FIGURE 56.3 The anatomy of the medial perforating veins of the leg. PTVs = posterior tibial veins, SPC = superficial posterior compartment.[40]

deep posterior compartment, behind the paratibial fascia (see Figure 56.3). This has to be incised before identification and division of the perforators can be accomplished. The medial insertion of the soleus muscle on the tibia may also have to be exposed to visualize proximal paratibial perforators. The paratibial fasciotomy can aid in distal exposure, but reaching retromalleolar Cockett I perforator endoscopically is usually not possible, and if incompetent, may require a separate small incision over it to gain direct exposure.

After completion of the endoscopic portion of the procedure the instruments and ports are removed, the CO_2 is manually expressed from the limb. Twenty ml of 0.5% marcain solution is instilled into the subfascial space for postoperative pain control. The tourniquet can be left inflated during the time stab avulsion of varicosities is performed on the foot, ankle, or calf. After deflating the tourniquet, laser or radiofrequency ablation or, occasionally, high ligation and stripping of the great or small saphenous vein, if incompetent, is performed. All stab wounds and the area

surrounding the saphenous vein is infiltrated with tumescent diluted anesthetic solution. The port sites are closed in two layers with dissolvable sutures, the stab wounds are closed with paper tapes and the limb is wrapped with an elastic bandage. A single dose of low molecular weight heparin is given subcutaneously during the procedure to decrease the risk of perioperative deep vein thrombosis. Elevation is maintained at 30 degrees postoperatively for three hours after which ambulation is permitted. SEPS is an outpatient procedure and patients are discharged the same day or within 24 hours following overnight observation. In the long term they are instructed to use firm compression (30 to 40 mmHg) elastic garment.

RESULTS OF SEPS

Experience with SEPS continues to grow and results from several centers are summarized in Table 56.1. The safety and efficacy of SEPS has been established in the North American SEPS Registry[17,24] and in nonrandomized case series.[2–16,18–23] In a randomized trial SEPS had a lower wound complication rate (0%) than traditional open surgical techniques (53%) at 21 months after surgery.[25]

The North American SEPS (NASEPS) registry compiled data from 146 patients, 101 of whom had active ulcers (C6) at the time of operation (see Figures 56.4 and 56.5).[17,24] Wound complication rate was 6%, and one deep venous thrombosis occurred at two months after surgery. The mid-term (24 months) results of the NASEPS registry demonstrated an 88% cumulative ulcer healing rate at one year. The median time to ulcer healing was 54 days. Cumulative rate of ulcer recurrence was significant: 16% at one year, 28% at two years, but still compared favorably to results of nonoperative management. Higher rate of ulcer healing was observed in those who underwent SEPS with saphenous vein stripping, compared to limbs that underwent SEPS alone; three- and 12-month cumulative ulcer healing rates of 76% and 100% versus 45% and 83% ($P < 0.01$), respectively.

In a prospective study Nelzen et al. reported on results of 149 SEPS procedures in 138 patients.[19] Forty-five percent of limbs had venous ulceration (C6–36 limbs, C5–31 limbs) and deep venous insufficiency was present in 7% of limbs. During a median follow-up of 32 months, 32 of 36 ulcers healed, more than half (19/36) within one month. Three ulcers recurred, one of which subsequently healed during follow-up. At a median follow-up of seven months following surgery, 91% of patients were satisfied with the results of the operation.

Our results at Mayo Clinic were reported by Kalra et al.[21] One-hundred and three consecutive SEPS procedures were performed over a seven-year period. Venous ulceration affected 74% of limbs (C6–42 limbs, C5–34 limbs), and deep venous incompetence was present in 89% of limbs. On life-table analysis 30-, 60-, and 90-day cumulative ulcer healing rates were 41%, 71%, and 80% with a median time to ulcer healing of 35 days. These results compare favorably with the 65% ulcer healing rates at six months, reported in the ESCHAR study that randomized patients to conservative management versus superficial venous surgery.[26] Mean follow-up in the SEPS study at Mayo was 3.25 years and one-, three-, and five-year cumulative ulcer recurrence rates were 4%, 20%, and 27% (see Figure 56.6).

In the most recent report from the Mayo Clinic, Puggioni et al. demonstrated excellent healing rates after SEPS in patients without previous deep vein thrombosis.[27] Eighty-eight SEPS procedures were performed in 81 patients with active (n = 50) or healed (n = 38) ulcers. Median follow-up was 35 months. Forty-four ulcers healed for a crude ulcer healing rate of 88%. Median time to ulcer healing

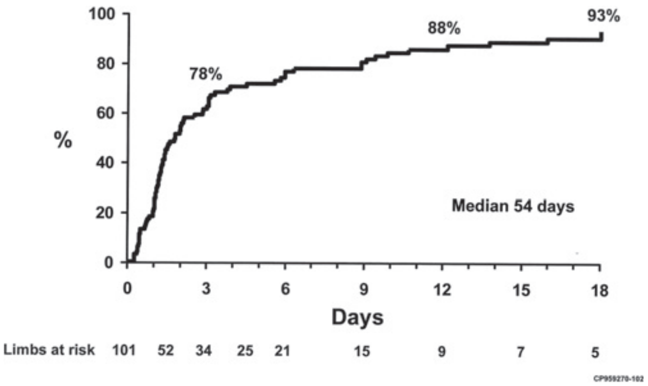

FIGURE 56.4 Cumulative ulcer healing in 101 patients after subfascial endoscopic perforator vein surgery. The 90-day, 1-year, and 1.5-year healing rates are indicated. The standard error is less than 10% at all time points.[24]

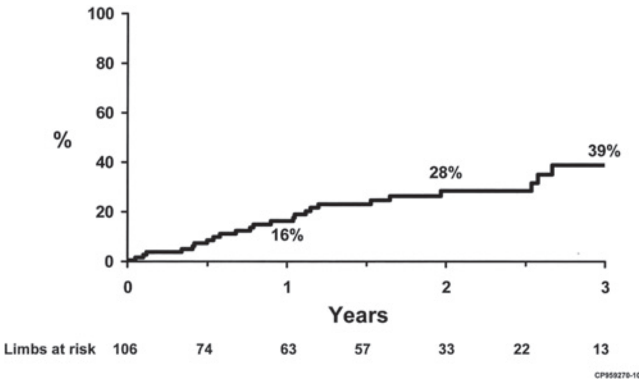

FIGURE 56.5 Cumulative ulcer recurrence in 106 patients of the North American Registry after subfascial endoscopic perforator vein surgery (SEPS). The 1-, 2-, and 3-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points.[24]

TABLE 56.1 Published Results of Subfascial Endoscopic Perforator Vein Surgery (SEPS)*

First author, year	Limbs (No.)	Limbs with history of ulcer (No.)**	Limbs with active ulcer (No.) φ	Saphenous ablation (%)	Wound dehiscence/ seroma (No.)	Hematoma (No.)	Paresthesia (No.)	Infection/ cellulitis/ thrombophlebitis (No.)	Ulcer healing %	Limbs with ulcer recurrence (No.) ϕ	Mean follow-up (months)
Jugenheimer and Junginger[4] 1992	103	NR	17	NR	3	6	10	0	94	0	27
Pierik et al.[29] 1995	40	40	16	10	0	0	0	3	100	1	46
Bergan et al.[9] 1996	31	25	15	100	2	2	0	6	93	0	NR
Rhodes et al.[30] 1998	31	25	12	77	3	2	2	2	100	1	11
Gloviczki et al.[17] 1999	146	122	101	60	0	0	10	5	84	26	24
Lee et al.[31] 2001	36	19	NR	92	0	0	2	4	89	2	14
Sybrandy et al.[20] 2001	20	20	20	70	0	0	0	0	85	2	46
Baron et al.[32] 2001	45	45	37	40	0	0	0	0	89	0	10
Iafrati et al.[33] 2002	51	51	29	55	1	2	0	0	74	7	38
Ciostek et al.[34] 2002	146	74	36	90	0	0	19	5	86	11	56
Kalra et al.[21] 2002	103	76	42	72	5	5	4	14	90	21	39
Bianchi et al.[35] 2003	74	74	58	77	0	3	0	9	91	4	44

*From Reference 38, with permission
**CEAP Classes 5 and 6
φ Disease Class 6
ϕ Recurrence calculated for Class 5 and 6

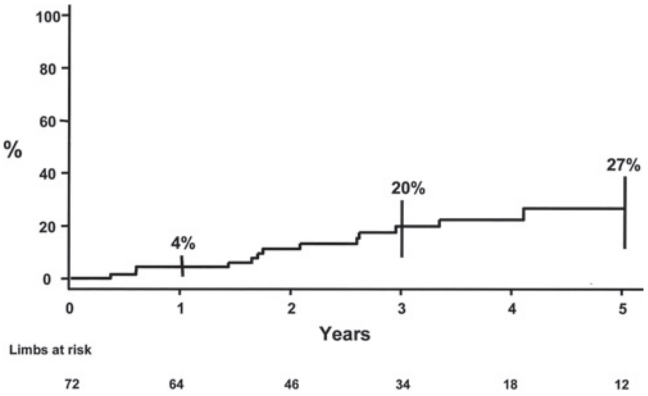

FIGURE 56.6 Cumulative ulcer recurrence in 72 patients in the Mayo Clinic series after subfascial endoscopic perforator vein surgery (SEPS). The 1-, 3-, and 5-year recurrence rates are indicated. All class 5 limbs at the time of SEPS and class 6 limbs that subsequently healed are included. The start point (day 0) for time to recurrence in class 6 patients was the date of initial ulcer healing. The standard error is less than 10% at all time points.[21]

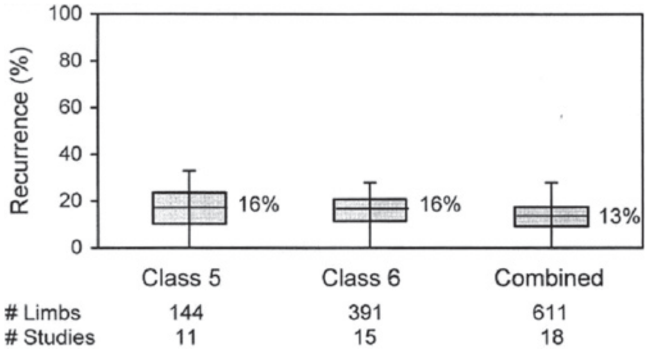

FIGURE 56.7 Cumulative ulcer recurrence after subfascial endoscopic perforator surgery (SEPS) in a meta-analysis of 611 limbs with C5 and C6 disease. *Horizontal lines*, point estimates; *boxes*, 95% confidence intervals; *error bars*, ranges for individual studies that contributed to each estimate; *class 5*, recurrence in limbs with class 5 disease at SEPS; *class 6*, recurrence in limbs with class 6 disease at SEPS in which ulcers subsequently healed; *combined*, recurrence in limbs with class 5 and class 6 disease. Number of limbs and studies in class 5 and class 6 disease do not total those in the combined group, because not all studies reported data separately for limbs with class 5 and class 6 disease.[36]

was 35 days, 90- and one-year cumulative ulcer healing rates were 79% and 88%. All six ulcers that did not heal by the time of last follow-up had previous deep vein thrombosis. Ulcer healing in post-thrombotic limbs at one year was 73% versus 100% in primary valvular incompetence (p = 0.02). Not surprisingly, healing rates were higher in those patients who had SEPS with superficial ablation versus those who had SEPS alone. Also, limbs with femoropopliteal reflux have decreased healing rates. SEPS with or without ablation of the incompetent superficial system was effective in decreasing ulcer recurrence as well. Eighteen ulcers recurred during follow-up, for an overall crude ulcer recurrence rate of 18/82 (22%). Freedom from ulcer recurrence at one, two, and five years were 96%, 90%, and 74%. Patients with primary valvular incompetence did very well, with freedom from ulcer recurrence at the same time intervals of 98%, 94%, and 85%, versus rates in post-thrombotic syndrome of 90%, 78%, and 50% (p = .06). Factors associated with ulcer recurrence were active smoking and a previous deep venous thrombosis.

Hemodynamic improvement after SEPS was previously reported by Rhodes and colleagues used strain-gauge plethysmography to quantitate calf muscle pump function and venous incompetence before and after SEPS.[15] The authors observed significant improvement in both calf muscle pump function and venous incompetence in 31 limbs studied within six months after SEPS. Twenty-four of the 31 limbs underwent saphenous stripping in addition to SEPS. Normalization of venous incompetence occurred in up to 50% of limbs studied, and this improvement was associated with a favorable clinical outcome. Although limbs undergoing SEPS alone had significant clinical benefits, the hemodynamic improvements did not reach statistical significance. This is likely related to both the small number of patients and the predominance of post-thrombotic syndrome in this subgroup.

Patients with primary valvular incompetence have better clinical outcome and also significantly better hemodynamic improvement compared with post-thrombotic limbs. Proebstle et al. using light reflection rheography before and eight weeks following SEPS showed significant improvement in limbs with primary valvular incompetence.[16] Using foot volumetry, Stacey and coworkers demonstrated that perforator vein ligation with ablation of saphenous reflux improved calf muscle pump function in limbs with primary valvular incompetence, although the relative expelled volume did not return to normal.[28] However, no hemodynamic benefit was found in post-thrombotic limbs.

Although the role of SEPS in post-thrombotic syndrome remains controversial, most patients still show marked symptomatic improvement in disability (pain and swelling), when assessed with the venous clinical scores.[21] Also, recurrent ulcers are usually smaller, more superficial, single more often than multiple, and heal again easily with conservative management.

In a meta-analysis of 20 published studies on SEPS, Tenbrook et al. analyzed the benefits and risks of surgical treatment in 1140 limbs with advanced chronic venous insufficiency.[36] After SEPS, with or without superficial venous ablation, ulcers in 88% of limbs healed. The recurrence rate in 611 limbs was 13% at a mean time of 21 months (see Figure 56.7). Risk factors for no healing and recurrent ulcers included new or recurrent incompetent perforator veins, post-thrombotic syndrome, deep vein obstruction and ulcers larger than 2 cm in diameter. Surgical complications included wound infection (6%), hematoma

(9%), neuralgia (7%), and deep venous thrombosis (1%). Randomized controlled trials are still needed to define the role of SEPS in the treatment of venous ulcer disease. Unpublished data of the Dutch randomized trial indicate benefits of SEPS in patients with large medial ulcers, in those with recurrent ulcers, and in patients who undergo the SEPS procedure in expert venous centers.[37]

CONCLUSIONS

Initial exuberance with SEPS focused much needed attention to chronic venous disease and the underlying venous anatomy and pathophysiology. Limitations of perforator ablations alone in treating patients with ulcers were also soon recognized. Without doubt, SEPS should be combined with ablation of the incompetent superficial system, performed either as staged or as combined procedures. Results have been excellent on both ulcer healing and recurrence in primary valvular incompetence without associated femoropopliteal reflux, but long-term ulcer healing could not be achieved in half of the operated patients with post-thrombotic syndrome. Incompetent perforators are but one of the contributing factors to ambulatory venous hypertension, and in patients with post-thrombotic syndrome and deep vein occlusion they likely are important outflow channels that should be preserved to assure the collateral venous circulation. Introduction of less invasive techniques for perforator ablation, such as ultrasound-guided sclerotherapy or radiofrequency ablation may diminish the role of SEPS in the future but results should be compared and analyzed before we diminish the use of a safe and effective endoscopic technique for ablation of the perforating veins.

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CHAPTER

57

Ultrasound-Guided Sclerotherapy (USGS) of Perforating Veins in Chronic Venous Insufficiency

FEDOR LURIE, ALESSANDRA PUGGIONI, and ROBERT L. KISTNER

Correction of clinically important hemodynamic abnormalities, such as reflux and obstruction, is the major treatment objective in patients with chronic venous disease. Achieving this goal theoretically should convert the patient into being asymptomatic, eliminate or reverse existing signs, and prevent progression to more advanced stages of venous disease. Practical challenges that face the surgeon who will treat a patient with chronic venous disease include selection of which vein to treat and which technique to employ.

Recent development of new treatment options for reflux in the superficial venous system have established a new standard when patients can be treated in the office without a need for general anesthesia, can ambulate immediately after treatment, have insignificant post-operative pain, and have almost no negative impact on quality of life immediately after treatment. At the time when venous stripping was the only choice for patients with saphenous insufficiency, surgical interruption of perforating veins either by subfascial endoscopic surgery (SEPS) or through small incisions was considered minimally invasive. In a new clinical environment, invasiveness and wound complication risk of these surgical techniques exceeds that of treatment of saphenous veins.

This chapter presents a review of a nonsurgical treatment option for incompetent perforating veins, ultrasound-guided sclerotherapy, which combines the precision of surgical approach with minimal invasiveness of an injection.

HISTORICAL PERSPECTIVE

The first description of the perforating veins of the lower extremities is attributed to JC Von Loder, a German anatomist who worked at the end of the eighteenth century,[1] but it was not until the work of John Homans when the role of incompetent perforators was postulated followed by development of surgical treatment.[2] After the precise definition of principles for perforator control was formulated in the 1930s by Robert R. Linton of Boston, and detailed investigations were performed by Frank Cockett of London, their modifications of perforator ligation became a universally accepted component of treatment of chronic venous disease. In the 1970s, DePalma and Edwards independently introduced a minimally invasive approach to perforator treatment addressing the problem of wound complications after subfascial ligation of incompetent perforators. Popularization of endoscopy in surgery inspired development of SEPS.[3,4] Incidence of wound complications was significantly decreased with SEPS, but the presence of other complications, such as deep venous thrombosis (less than 1%), superficial thrombophlebitis (3%), and saphenous neuralgia (7%),[5,6] as well as the technical complexity of the SEPS procedure and its high cost, stimulated interest in alternative techniques.

Compression sclerotherapy of incompetent perforating veins was introduced by Fegan in the 1950s.[7] He first hypothesized that, in order for this technique to be effective, patients must continuously wear postoperative compressive bandages. In one of his late publications, in 1979,[8] he reported on how "the success of injection compression sclerotherapy depends on the facts: (1) that in the majority of patients with varicose veins and, in almost all those with symptoms incompetent perforating veins are present; and (2) that if these incompetent perforating veins are permanently occluded the superficial veins, no longer subjected to an abnormal blood flow, are capable of regaining their normal tone and diameter and the valves in them regain their competence. The aim of the injection technique is to prevent abnormal pressures and retrograde flow from the deep to the superficial venous system."

With growing popularity of sclerotherapy different techniques have been developed.[9] Results, however, were often unsatisfactory. In 1981 Cockett summarized main causes of failure in perforator injection as (1) inability to accurately locate the perforator, (2) potential damage by extravascular injection of sclerosant, (3) potential damage to posterior tibial artery, and (4) potential damage to deep veins causing DVT.[10]

Advances in ultrasound imaging in the 1980s and 1990s provided the technical basis for ultrasound-guided procedures. At the same time, reliable identification of perforating veins became not only possible, but was integrated into standard diagnostic protocols.[11] Together with new sclerosing agents, which can be effectively used in significantly lower con-centrations and less damaging to extravascular tissues, these advances helped to overcome the deficiencies of conventional sclerotherapy of perforating veins. By the late 1990s ultrasound-guided sclerotherapy (USGS) became popular in European countries and made its way to the United States.[12–15]

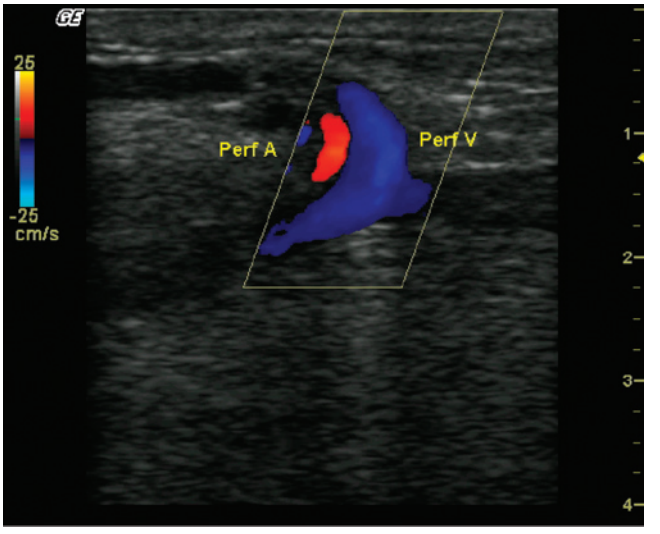

FIGURE 57.1 Perforating vessels. The perforating artery (Perf A) is located next to the perforating vein (Perf V) at the fascial opening.

BASIC CONSIDERATIONS

To perform echosclerotherapy of lower extremity perforating veins, a thorough knowledge of their anatomy and physiopathology is necessary. Perforator veins connect the superficial to the deep venous system and to the venous sinuses within the leg muscles. These veins usually contain a series of bicuspid valves, located in their subfascial segment, which prevent transmission of high pressure from the deep venous system into the superficial veins. The distribution of medial perforating veins connecting the superficial and deep systems in the calf and thigh is relatively constant. However, the number and anatomy of the numerous perforators to the muscular venous sinuses is unpredictable. Perforating veins are accompanied by perforating arteries supplying the skin and, sometimes, by cutaneous nerve branches and lymphatic vessels. Perforating arteries are usually smaller in diameter and located superior to the accompanied vein.[16] The presence of these arteries can often be confirmed by duplex scan[17] (see Figure 57.1).

The coexistence of perforating veins and arteries in the lower extremities was described first by Robert Linton who established that "communicating" pedicles have venous and arterial components. He also described how these vessels run along the intermuscular fascial planes and that "the arteries are so small that it is not necessary to preserve them." Identification of the perforating arteries, although not always possible, becomes desirable when ultrasound-guided sclerotherapy of perforating veins is performed. Accidental injection of sclerosing agent into the arterial bed may possibly cause complications such as skin necrosis, and can be prevented by visual control, or by performing injections at a distance from the fascial opening where the perforating artery and vein are not in such close proximity to each other. The role of perforator arteries in pathogenesis of venous ulcers and sanogenesis after treatment is yet to be studied. As they provide blood supply to skin areas affected by venous disease, preservation of these vascular structures during treatment may be desirable. Our observations indicate that blood flow in perforating arteries increases after USGS.[17] If this hyperemia can be shown to be beneficial in ulcer healing, selective oblation of perforator veins by USGS could be more desirable than surgical interruption when both veins and arteries are interrupted. The same logic may be applied to perforating cutaneous nerves.

Perforator vein incompetence usually is associated with deep and/or superficial venous incompetence, but, if left untreated, can persist after successful treatment of saphenous reflux. Strong association of perforator incompetence with skin changes and ulceration has been well established, however, incompetent perforators are often present in less advanced stages of the disease, when their role in disease progression or/and recurrence of varicose veins is less obvious. Following the cases of persistent perforator veins after correction of other sources of reflux at Straub Clinic revealed association of patients' symptoms with isolated incompetent perforators, and relief of these symptoms after successful USGS. These findings and variations in anatomy support identification of not only perforator veins in areas of skin changes, but all those potentially clinically important as a treatment target.

Incompetent perforating veins 4 to 7 mm in diameter can be treated with this technique. Smaller veins seldom are incompetent, and larger veins require larger volumes of

sclerosant, which potentially increases the risk of complications.

CLINICAL CONSIDERATIONS

Indications for USGS are not different from indications to surgical interruption of perforating veins. Cases of symptomatic chronic venous disease from C2 to C6 clinical class (CEAP) that have demonstrable incompetent perforating veins at duplex ultrasound constitute the majority of indications. In primary disease, USGS can be performed at the time of initial treatment of saphenous reflux, or as a separate stage. In secondary (post-thrombotic) disease, careful consideration should be given to the pathophysiologic role of incompetent perforator in each individual extremity. Incompetent perforators can constitute a major outflow track around an obstructed segment in some cases and be a contributor to skin ulceration in others.

USGS does not require anesthesia and can be performed in the office as well as in the operating room.

Patients with known allergic reactions to sclerotherapy agents, or who are pregnant or lactating should be excluded. The presence of severe arterial occlusive disease or active vasculitis is also a contraindication as inadvertent intra-arterial injection potentially can result in limb loss.

Sclerosing Agents

Sodium Tetradecyl Sulphate (Sotradecol®) and Sodium Morrhuate are the agents frequently used for therapy of incompetent perforating veins. Polidocanol (Aethoxysklerol®) is another valid drug for this purpose still waiting for FDA approval in the United States.

The mechanism of action of all these drugs is based on their detergent properties. Immediately after injection the endothelial cells, in contact with the drug, undergo swelling and disruption. This irreversible trauma causes localized thrombosis, vasospasm, and then vein fibrosis and reabsorbtion. Larger veins should be treated with increased concentrations rather than larger volumes, since this may cause escape of the drug into the deep veins and potentially into the systemic venous circulation.

Recent development of foam sclerotherapy opens new opportunities for treatment of perforating veins. In addition to different sclerosing agents and their concentrations, the use of foam introduces variability in type of gas, gas-to-liquid ratio, time between processing and use, size of the bubbles, and methods of preparation. This variability complicates analysis of results and development of guidelines. Until the standardization of sclerosing foams is developed, foam sclerotherapy continues to be based on the experience and preferences of a treating physician.

PREOPERATIVE DUPLEX

Duplex ultrasound scan plays the most important role in evaluation of the patient before USGS. Complete examination of deep and superficial venous systems including testing for obstruction and valvular incompetence is necessary in every case. Perforating veins should be identified by scanning all aspects of the calf and by following the course of the Great Saphenous vein (GSV), the Giacomini vein, or any incompetent nonsaphenous vein of the thigh. It is preferable to examine patients in a standing position as the increased hydrostatic pressure makes perforating veins easier to visualize and evaluate. Incompetence of a perforating vein can be determined by registering of reversed flow (directed to the superficial veins) longer than 0.4 seconds, or by the size of the vein at the fascial opening exceeding 3.5 mm, or by the presence of both criteria.[11,18]

In addition to identification of incompetent perforator veins, ultrasound provides information on which veins are connected by these perforators, and thus allocates each perforator to a defined place in the hemodynamic map of the venous system of the affected extremity. At the time of duplex scan, incompetent perforating veins located in the areas of skin changes and ulcers, those connected with corona phlebectatica, or clusters of varicose veins, and those associated with symptoms should be separated from perforators found in asymptomatic limbs, and from those with a questionable hemodynamic role in the disease process. This information is crucial for development of a surgical plan and for a decision on how to treat each of the incompetent perforators.

TECHNIQUE

The procedure can be performed under general or local anesthesia during saphenous and varicose vein ablation, or as an isolated procedure in the outpatient clinic setting. When performed as a standing alone procedure, no sedation or local anesthesia is required.

The procedure room is warmed to a comfortable temperature in order to avoid venous constriction and the patient is positioned in the supine or prone position, depending on the location of veins to be treated. The skin is prepped with Iodine solution and a sterile latex cover applied to the ultrasound probe. This must be oriented longitudinally and after the target vein is identified, a 25-gauge needle connected to a 3-cc syringe is inserted into the skin close to the ultrasound transducer. The needle tip has to be oriented toward the perforating vein, along the sagittal plane of the probe. The target for the injection is the segment of perforating vein above the fascia (see Figure 57.2a). A small amount of venous blood is withdrawn in the syringe to confirm the correct position of the needle and 1 to 2 cc of 1% Sodium Tetradecyl Sulphate,

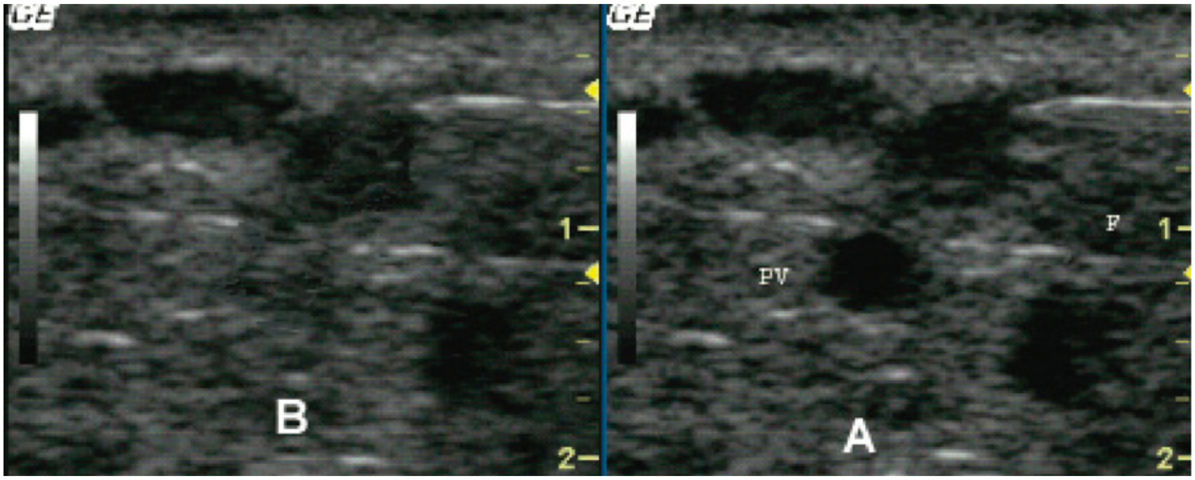

FIGURE 57.2 Ultrasound-guided sclerotherapy of the perforating vein. **A.** The needle is placed in a vein above the fascia (F). **B.** After an injection the perforating vein (PV) is filled with an echogenic material and has no flow.

or 5% Sodium Morrhuate is injected under duplex vision. The sclerosing agent can be easily seen by B-mode ultrasound imaging, thus monitoring each injection with ultrasound provides vital information regarding the precision of injection and volume of sclerosant needed to be injected to close the perforator, but not to cause damage of deep veins. Pain during injection, among other causes, can indicate that a perforating artery has been punctured, and therefore injection should be stopped to avoid serious complications.

The needle is withdrawn and compression applied for a few minutes. The vein is reimaged and sclerotherapy considered successful if no residual flow is observed in the treated perforator (see Figure 57.2b).

Larger veins can be treated by foam sclerotherapy. With this technique conventional sclerosing agent and air are mixed in order to form fine bubbles. The principle behind this method is that by displacing blood from the treated vein and increasing the contact time between the sclerosant and the vein more effective treatment can be achieved.

POSTOPERATIVE CARE

External compression is important for effective sclerotherapy. Even after a successful injection, inadequate compression of the treated area may allow blood flow through a damaged, thrombogenic endothelium and so thrombophlebitis may develop at that site. Furthermore, adequate compression may improve the calf muscle pump, thus preventing propagation of thrombus into the deep veins. Recurrences may be due to inadequate initial or subsequent continuous compression until a fibrous occlusion occurs. Elastic bandages are applied to the extremity and maintained for one to two weeks and replaced by class II-III knee-high compression stockings thereafter. Patients with heavy elastic bandages should be warned to remove them should pain occur, before ischemia has caused any damage. Patients are encouraged to ambulate in order to prevent venous stasis that may lead to deep venous thrombosis.

RESULTS

Although available reports on results of USGS consistently demonstrate benefits of this treatment modality, their conclusions should be taken with caution.[12–13,15,19–22]

Important differences between USGS and surgical interruption of perforating veins should be considered when clinical results of perforating vein treatment are analyzed. The true minimally invasive nature of USGS translates into minimal impact on patients' immediate post-treatment activity and quality of life. Early unrestricted ambulation can be a contributing factor for the treatment outcome.

Any surgical procedure, including SEPS, results in inflammation followed by scar formation in the area of the treated perforator. The impact of these processes on an extremity with CVD has not been defined, but presents theoretical possibilities either for prevention of development or recurrent perforators. Postoperative scars may act as a mechanical barrier against reconnection of deep and superficial system, but on the other hand, postoperative inflammation might promote neovascularization, thus recurrence of perforators. In case of USGS, the vein remains in place, therefore its recanalization is possible. Availability of information on objective documentation of immediate treatment success, and differentiation between reopening of treated perforator and development of new vessels can significantly impact interpretation of published data.

Utilization of different sclerosing agents in a variety of concentrations with differences in effects on the vein and

surrounding tissue contributes to the complexity of interpretation of reported results.

Waiting for a higher level of evidence on USGS success, and for more precise definitions of outcome measures, one can rely only on clinical experience of groups and individuals performing a high volume of these procedures. The Straub clinic group has performed over 3000 injections of incompetent perforators during the past five years.[15,19–21] Immediate successful obliteration of the treated veins at the time of injection was obtained in 98% of cases. Skin complications with superficial skin necrosis occurred in six patients. Recurrence, defined as the presence of flow in a previously sclerosed perforating vein at duplex follow-up, was present in 23% of cases with a mean follow-up of 17 months. Venous clinical severity scores decreased on average from 11.95 pretreatment to 6.5 posttreatment ($p < 0.05$). Likewise, venous disability scores dropped from 1.86 pretreatment to 0.81 posttreatment ($p < 0.05$). Perforator recurrence was more common in limbs with ulcerations. Except for the rare occurrence of skin necrosis, cosmetic results were excellent, often with partial reversal of preexisting skin changes, and relief of symptoms.

COMPLICATIONS

Sclerotherapy of perforating veins is associated with minimal discomfort and pain and thus does not require local or general anesthesia. Occurrence of immediate or delayed pain at the site of injection or in a larger calf region should alert the operator against extravascular injection in the soft tissue or in a nearby artery. Intra-arterial injection is extremely painful, whereas extravasation in the subcutaneous tissue may remain asymptomatic, unless the sclerosant solution had been mixed with normal saline, or a high concentration of sclerosant had been used. As a result of extravasation, superficial skin necrosis may occur. In our experience superficial skin necrosis occurred in less than 2% of patients, and usually resolved with minimal sequelae in a matter of weeks. A more serious complication is intra-arterial injection as this produces a diffuse endotheliitis blocking the arterioles, which may lead to tissue ischemia and gangrene. Should this complication occur, injection of procaine around the injected artery, local cooling, systemic heparinization, and infusion with low-molecular-weight dextran are recommended.

As discussed previously, a potential complication of inadequate compression is thrombophlebitis, because residual flow within a damaged vein predisposes to thrombosis of the vein and eventual recanalization. Deep venous thrombosis is also rare, probably due to injection of large volumes of sclerosant. Again, if sclerosing agents are injected in small amounts, only the intima, not the blood, should be affected. These agents are inactivated rapidly by the blood and are, paradoxically, hemolytic and not thrombotic. Another important point to stress is that patients must be encouraged to walk immediately after treatment and must continue this every day to prevent stagnant blood from collecting in the damaged veins.

It would be more prudent to avoid injecting limbs of patients with known congenital or acquired phrothrombotic state (bedridden, neoplastic, early postthrombosis).

Another possible, although rare, serious complication is anaphylactic shock. While performing injection sclerotherapy, all the necessary equipment to handle this situation must be readily available (oxygen, epinephrine, and steroids) as this could be a life-threatening event. We have not observed this complication during perforating vein sclerotherapy.

CONCLUSION

Ultrasound-guided sclerotherapy is a minimally invasive, alternative technique for the treatment of incompetent calf perforating veins. If a rigorous technique and careful precautions are undertaken, minimal complication rate and satisfactory clinical results can be achieved. After sclerotherapy patients can resume their routine activities and return to work, and this is with no doubt one of the most appealing aspects of this method. We believe that the adoption of this technique in experienced hands potentially could represent the standard method of treating incompetent perforators, as it is associated with minimal discomfort for the patient, acceptable recurrence rates, and is easily repeatable. These results are encouraging, but future research should define precise indications, optimal techniques, and measures for clinical and hemodynamic success for this procedure.

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CHAPTER

58

Perforating Veins

JOHN J. BERGAN and LUIGI PASCARELLA

INTRODUCTION

The development of ankle hyperpigmentation, edema, atrophie blanche, and incipient ulceration, the cutaneous trophic changes of chronic venous insufficiency (CVI), are linked to a complex microangiopathy.[1] This, on a macrovascular level is linked to ambulatory venous hypertension, which is enhanced by superficial and deep reflux. Also, it is linked to a lesser extent to venous obstruction. Thus it appears that venous hypertension is the fundamental pathogenic factor that leads to CVI.[2]

Valve Remodeling Produces Distal Venous Hypertension

Our observations on ultrasound proven, refluxing saphenous veins have shown that the endothelium of their venous valves and vein walls contain an infiltration of monocytes and an associated increased expression of adhesion molecules (ICAM-1). There is a statistically significant spatial correlation between CD68-positive monocytes and ICAM-1 in the various tissue areas of the valves and the vein walls.[3] The leukocytes and the expression of adhesion molecules is concentrated more so on the proximal venous wall and valve cusp than on the distal wall and leaflet. This suggests a cause and effect relationship with venous hypertension.

The altered hemodynamics that accompany the venous hypertension change the plasma sheer stress, which, in turn, stimulates leukocyte pseudopod projection and adhesion of the leukocytes to the endothelium. It is a reduction, not an increase, in shear stress that leads to adhesion of the white cells on the endothelium.[4] Adhesion of the cells is followed by migration through the endothelium and interstitial macrophage infiltration.

The microscopic alterations, linked to venous hypertension described earlier are accompanied by gross tissue changes, which result in valve incompetency. Observations of these changes in primary venous insufficiency reveal dilation of the valvular annulus, atrophy of the cusp, and fibrotic remodeling of the valve and its annulus. Some have proposed that hemodynamic mechanical injury increases tissue damage to the annulus and cusps.[5] Others suggest that activated leukocytes release transforming growth factor-β_1 (TGF-β_1) gene expression, which alters environmental protein production.[6] This might explain the gross observations seen in affected valves.

Venous Stasis: An Inappropriate Term

Although the term chronic venous insufficiency (CVI) is in common usage and is becoming increasingly visible, the older term, venous stasis remains dominant. This is a tribute to John Homans of Harvard, who introduced the concept that venous stasis was the ultimate cause of venous ulceration.

Homans believed that there was a causal relation between venous ulcerations of the legs and blood stasis in patients with severe chronic venous insufficiency.[7] Blood stasis, as proposed by Homans, was determined by a shortage of oxygen content in the skin, and it was this that led to a condition of tissue hypoxia, necrosis, and ulceration.[7] Many observations in the last quarter century have demonstrated that shortage of oxygen is not the main cause of venous ulcers.

It has been hypothesized that presence of cutaneous arteriovenous fistulas might cause a deprivation of oxygen by shunting oxygenated blood away from skin already hypoxic from stasis. Such arteriovenous connections are easily demonstrated[8] by arteriography and microdissection

in limbs with severe CVI but are not thought to contribute to the skin changes.[9] Coleridge Smith and others have shown that the content of oxygen in the skin and in varicose veins of limbs with venous ulcers is not decreased.[10] In fact, oxygen content in varicose veins is increased.[11] In addition the oxygen diffusion defects suspected by histological findings of pericapillary fibrin cuffs have been refuted. Studies such as clearance of Xenon133 through liposclerotic skin have shown no significant oxygen barrier.[12]

PREULCERATIVE CUTANEOUS CHANGES

Inflammation dominates the early skin changes that precede venous ulceration. Increased leukocyte activation and an increased expression of soluble adhesion molecules have been demonstrated. There is a perivascular infiltration of the papillary plexus capillaries. Granulation tissue composed of lymphocytes, plasma cells, macrophages, histiocytes, and fibroblasts invades the subepithelial layer. This granulation tissue is responsible for the deposition of collagen fibers.[13] Collagen fibers appear to have completely lost their normal orientation in the cutaneous tissue. These lesions account for the inflammatory and post-inflammatory process of tissue fibrosclerosis: lipodermatosclerosis.

When skin at the border of chronic venous insufficiency is compared to normal skin in the same individual, the strong expression of ICAM-1 is seen in addition to a dense infiltration by T lymphocytes and macrophages. In some instances, the tissue also is infiltrated by an increased number of mast cells.[14] This is the typical picture of a chronic inflammatory reaction with an upregulation of endothelial adhesion molecules and dermal infiltration by T lymphocytes and macrophages in the skin of patients with CVI.

The Perforating Veins

Incompetent perforating veins are strongly associated with superficial venous reflux, and it is still controversial whether incompetent perforating veins are the primary cause of skin changes of chronic venous insufficiency or whether the incompetent perforating veins and skin changes are the result of superficial reflux. The cause of valvular dysfunction in perforating veins is not yet fully understood (see Figure 58.1).

Despite the classic studies of Linton[15] and Cockett,[16] it is still not known what the exact role of incompetent perforating veins is in the development of venous ulceration. Our observations suggest that venous hypertension is closely associated with valve damage and remodeling, which produces subsequent valve incompetence.[17] Therefore, it is useful to relate these findings to the valves in perforating veins.

It is well known that muscle contraction produces muscular compartment pressures in the range of 100 mm mercury and higher.[18] Such pressures exerted over time could initiate the cascade of molecular events, which eventuate in valvular incompetence. This valve incompetence would then produce the cutaneous "blow out" described as "spherical dilatations on veins under the skin" by Dodd and Cockett.[19] Failure of perforating vein valves due to their remodeling caused by repetitive compartment pressure elevation induced by normal exercise would lead to the skin changes described earlier.

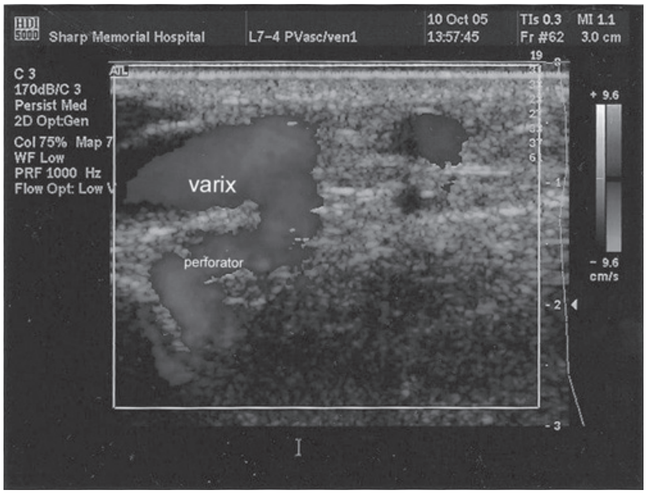

FIGURE 58.1 This reproduction of an ultrasound scan shows a perforating vein penetrating the deep fascia and refluxing into a nonsaphenous varix. It is calf muscle contraction that provides the pressure that is transmitted through a failed valve and elongates and dilates the superficial vein thus converting it into a varix.

A NEW HYPOTHESIS

A useful hypothesis is that venous hypertension, caused by superficial reflux and calf compartment pressure, is transmitted to unsupported venules of the skin. It is this sum of gravitational and hemodynamic pressure that stimulates the skin changes of chronic venous insufficiency. If this is true, a large component of ankle venous hypertension emanates from normal calf exercise with calf compartment pressures transmitted directly through the incompetent perforating vein valves to the skin (see Figure 58.2).

Indirect evidence of the importance of perforator veins in venous ulceration comes from surgical experience in dividing perforating veins in treatment of CVI.[20] A shorter ulcer healing time and improved hemodynamics have been found in limbs subjected to perforating vein surgery.[21]

De Palma showed in a crossover study that failure of conservative care, mainly consisting of compression, could be reversed by intervention with division of perforating veins.[22] This report, much like others,[23] is confused by the fact that 70% of the limbs had simultaneous stripping of the long saphenous vein at the time of perforator vein interrup-

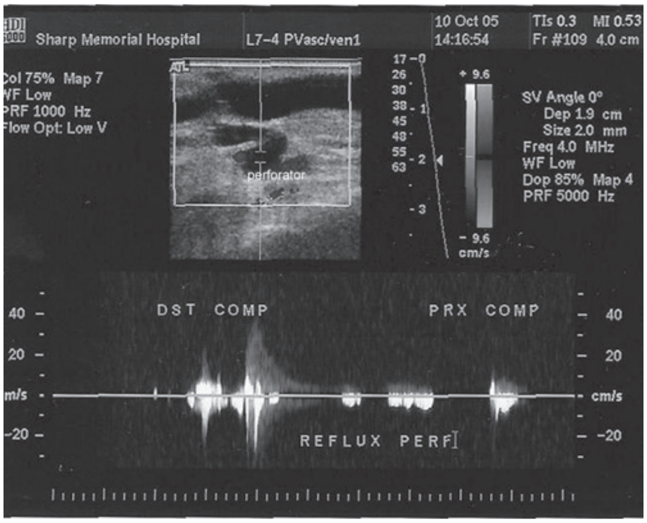

FIGURE 58.2 This perforating vein is shown penetrating the deep fascia. It is elongated and tortuous. It is dilated as well. Its outward flow is demonstrated best by compression of distal soft tissues.

TABLE 58.1 Hypothesis Explaining Genesis of Advanced Chronic Venous Insufficiency

1. Superficial vein valve incompetence* raises distal venous pressure.
2. Perforating vein valve incompetence** raises distal venous pressure.
3. Additive effects of superficial and perforator incompetence produce profound distal venous hypertension.
4. Venous hypertension produces venulectasia, edema, leukocyte-endothelial interaction, and the inflammatory response.
5. Inflammation produces hyperpigmentation, fibrosis, and ulceration.

*Due to gravitational reflux induced valve remodeling.
**Due to muscle compartment pressure induced valve remodeling.

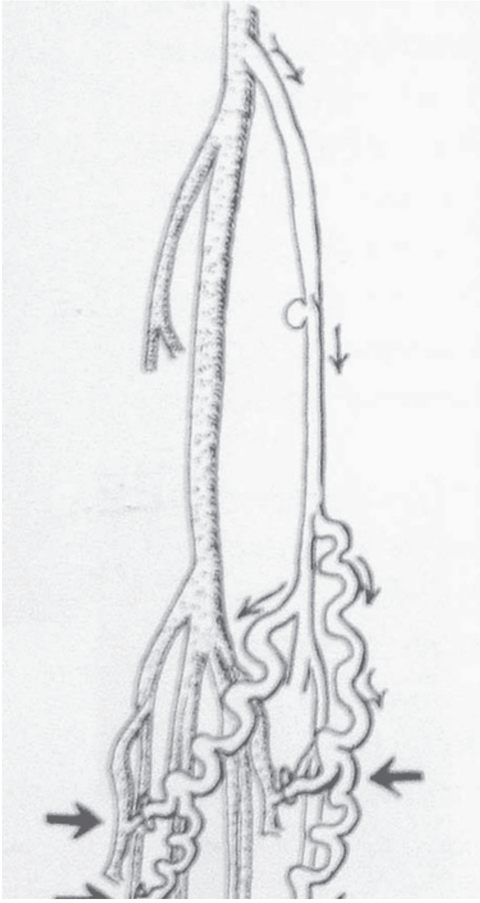

FIGURE 58.3 Normal perforating vein blood flow is from the superficial to the deep venous system. When saphenous vein reflux and varicose veins are present, the direction of flow is normal but the perforating veins which allow reentry of reflux flow may enlarge and become incompetent as shown in this diagram. (From Reference 27, with permission.)

tion. In fact, the sum of these two maneuvers did reduce venous hypertensive microangiopathy.

As ancient theories of causation of CVI gradually have been disproven as indicated earlier, it is no longer thought that venous blood stasis or ischemia due to a-v fistulas, fibrin cuff development, or leukocyte trappings are important. Instead, a more logical explanation of the skin changes of chronic venous insufficiency is credible (see Table 58.1).

In development of the severe changes of CVI, first, venous hypertension and superficial venous valve failure are linked.[21] Sequential venous valve failure may be centrifugal or centripital. This allows venous hypertension to be transmitted to the ankle by superficial reflux. Next, perforating vein valves fail through the same mechanisms of venous hypertension-induced valve remodeling. Or, perforating veins acting as part of the private reflux recirculation can enlarge to the point of valvular incompetence[22] (see Figure 58.3).

Subsequent to perforating vein valve failure, subcutaneous changes of inflammation are produced by the inflammatory process,[14] and these lead to the clinical manifestations of chronic venous insufficiency.

As suggested previously, therapy of CVI supports this hypothesis. Compression treatment reduces ambulatory venous pressure and is effective in healing venous leg ulcers.[24] Superficial vein surgery reduces ambulatory venous pressure, allows healing of venous leg ulcer, and reduces the effects of CVI.[25] Perforator vein interruption by the Linton or endoscopic techniques reduces ambulatory venous pressure and ameliorates the chronic changes of CVI.[26,27]

EXIT AND REENTRY PERFORATING VEINS

There are two fundamental facts that confuse understanding of perforating veins. The first relates to flow direction. Some perforating veins produce abnormal outflow from deep circulation to superficial circulation. This is demonstrated in Figure 58.1. This can be termed perforating vein

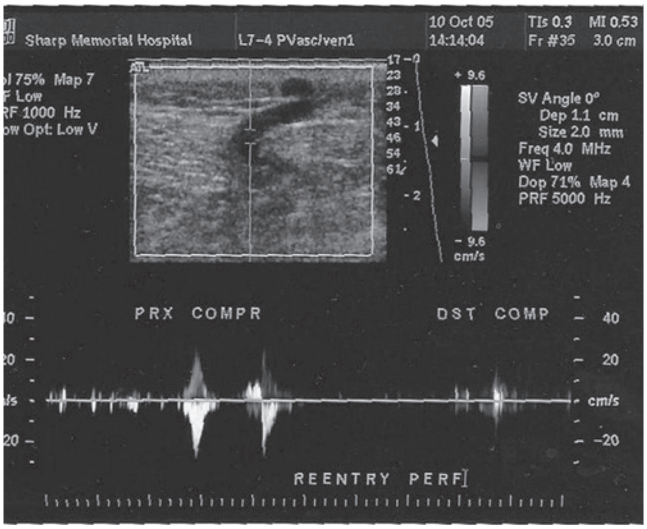

FIGURE 58.4 This reentry perforating vein has become tortuous because of increased flow. Distal compression causes its inward directed flow to stop. This resumes after distal compression release.

reflux. Other perforating veins demonstrate normal flow from the superficial system to the deep system. This is shown in the diagram of Figure 58.3 and the duplex scan shown in Figure 58.4. In situations of superficial venous incompetence and reflux, these can be called reentry perforating veins. It was Hach who understood this best, as he described the private circulation of reflux in superficial veins reentering to the deep system and the deep system in turn refluxing into the superficial veins.[24] It is most likely that it is the reentry perforating veins that disappear after adequately performed superficial venous stripping.

Another confusing factor in relating perforating veins to venous ulceration is the fact that venous ulceration is not directly related to severity of hemodynamic changes.[25] The lower limbs in a patient with bilaterally severe varicose veins might appear to be identical and might have identical hemodynamic measurements, but one limb might have all the stigmata of CVI and the other might have none. This is readily explained by the fact that skin changes are not caused by the venous hypertension or other hemodynamic changes but instead are dependent upon leukocyte activation and the subsequent molecular changes that follow. In the absence of leukocyte activation, skin changes do not occur.

However, it may very well be that perforating vein outflow or reflux as detected by color flow Doppler duplex on release of distal compression creates the hypertension in the subcutaneous venular network that elongates and dilates the capillaries, enlarges the intercellular junctions, produces edema, and triggers the inflammatory reaction that causes the skin changes.

If this is proven to be true, observations on the efficacy of measures to reduce cutaneous hypertension such as effective compression, superficial venous reflux ablation by foam sclerotherapy,[26] and perforator vein interruption will rest on a firm foundation. Even effective pharmacological intervention to moderate leukocyte activation is foreseeable.

CONCLUSIONS

Perforating veins and severe CVI are linked and descriptions of molecular events associated with venous hypertension explain the relationship. These validate current medical and surgical therapy and point the way toward more effective and less cumbersome treatments in the future.

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CHAPTER

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Importance, Etiology, and Diagnosis of Chronic Proximal Venous Outflow Obstruction

PETER NEGLÉN

In the complex make-up of the multifactorial etiology of chronic venous disease (CVD), the presence of venous obstruction largely has been ignored, while reflux has been emphasized. This is perhaps owing to the fact that an efficient treatment has not been available and the physiology of venous obstruction poorly understood. Since a critical venous outflow obstruction has not been defined, no accurate hemodynamic test has been developed. It is, however, well known that limbs with the combination of venous outflow obstruction and reflux fare worse than in the presence of either alone. This combination is seen in 55% of symptomatic patients with CVD and leads to the highest levels of venous pressure and the most severe symptoms.[1–5]

The iliac vein is the common outflow tract of the lower extremity, and chronic obstruction of this segment appears to result in more severe symptoms than does lower segmental blockage.[6,7] Distal obstructions are more readily compensated for, because of facilitated collateralization in the femoral-popliteal segment owing to the presence of double veins, direct connection to the profunda vein, sapheno-saphenous connection, and deep muscular tributaries in the thigh. Conversely, the collateral formation is relatively poor in the iliofemoral segment. Although the pelvic collaterals may appear large on venogram, they may be of little functional value. The flow is often retrograde due to reversed valve orientation and impeded due to the meandering course of the vessel. Interestingly, it has been shown by intravascular ultrasound (IVUS) that the average iliac venous stenosis was tighter in presence of collaterals than without. The rate of a significant obstruction as per preoperative pressure measurements were the same as in limbs with and without collaterals. One third of limbs had significant provoked femoral pressure differential; that is, positive hemodynamic test for obstruction, during surgery.[8] It appears that a presumed increased flow through collaterals did not adequately compensate for the outflow obstruction in all instances. The prevailing view that collateral formation compensates for a venous outflow obstruction, therefore, is challenged. These observations support the concept that pelvic collateral formation suggests the presence of a significant venous obstruction.

Symptoms of proximal chronic venous obstruction may vary greatly, ranging from moderate swelling and pain to discoloration and stasis ulcers. Symptoms are also influenced by any concomitant deep or superficial reflux. Obstruction plays an important role in the clinical expression of chronic venous disease, especially as pain. Negus et al. suggested that limb swelling and pain were related to the obstructive component whereas limb ulceration resulted from valve reflux.[9] Ulcer is rarely seen with isolated obstruction, and formation of ulcer appears to require presence of reflux.[3] Nevertheless, correction of outflow obstruction results in substantial symptom relief including ulcer healing. A substantial number of patients with CVD complain of disabling limb pain and swelling without skin changes.[10] The dominant pathophysiologic component in these patients may be obstruction rather than reflux, and it is possible that these symptoms are mainly attributable to the outflow blockage. "Venous claudication" is a condition described as an exercise-induced "tense" pain, which requires several minutes of rest and often leg elevation to achieve relief. Following iliofemoral thrombosis, venous claudication has been diagnosed by treadmill test in 44% of patients.[11] Certainly patients with significant outflow obstruction may have less dramatic symptoms with less distinct lower extremity pain and discomfort with decreased quality of life and moderate disability. We evaluated 4026 patients for CVD spanning all clinical severity classes (C in CEAP = C_{1-6}) during 1996 to 2004 and treated 879 patients for iliac vein obstruction with venous stenting (22%).

CHRONIC THROMBOTIC OBSTRUCTION

Poor recanalization following acute deep vein thrombosis is the most common cause of chronic venous blockage. Remaining obstruction is the principal cause of symptoms in approximately one-third of postthrombotic limbs.[4,5] In addition, it has been demonstrated that persistent obstruction of proximal veins is associated with progressive distal vein incompetence.[12,13] The most symptomatic outflow obstruction occurs following deep vein thrombosis involving the iliac segment. It may be limited to the iliofemoral segment or contiguous from the calf to the iliac veins. Approximately 20% of these iliac veins will completely recanalize on anticoagulation treatment, and the remaining veins recanalize partly and develop varying degrees of obstruction and collateral formation.[14,15] Recanalization appears to be inhibited and more incomplete when an external compression (e.g., left iliac vein compression) is present.[16] Cockett et al. observed that the obstructive lesion that precipitated the thrombosis impeded its resolution and the post-thrombotic perivenous fibrosis appeared to develop excessively at the initiating lesion site, the combination resulting in severe clinical presentation.[9,17] This observation is of great importance since it has been reported that 80% of limbs with iliofemoral DVT has underlying extrinsic iliac compression-type of lesions detected by spiral CT venography.[18] The remaining postthrombotic obstruction is often symptomatic. Five years after iliofemoral DVT is treated conservatively with anticoagulation, 90% of patients suffer symptoms of CVD. Debilitating venous claudication is found in 15 to 44% of patients and venous ulcer has developed in 15% of limbs.[11,14]

The typical post-thrombotic iliofemoral lesion often involves both common and external iliac veins with irregular stenosis or occlusions and axial, transpelvic, and ascending lumbar collaterals are present. More uncommon is the finding of a diffusely narrowed long segment of the iliac vein without any collateral formation. We have named it a Rokitansky stenosis, from the nineteenth century pathologist who described the phenomena (Fig. 59.1).[19] A perivenous fibrosis develops due to the periphlebitic inflammation following acute deep vein thrombosis. The chronic result is a fibrotic cylinder, which impedes any collateral development and expansion of the vein. Thus, significant outflow obstruction cannot be excluded because of lack of collaterals.

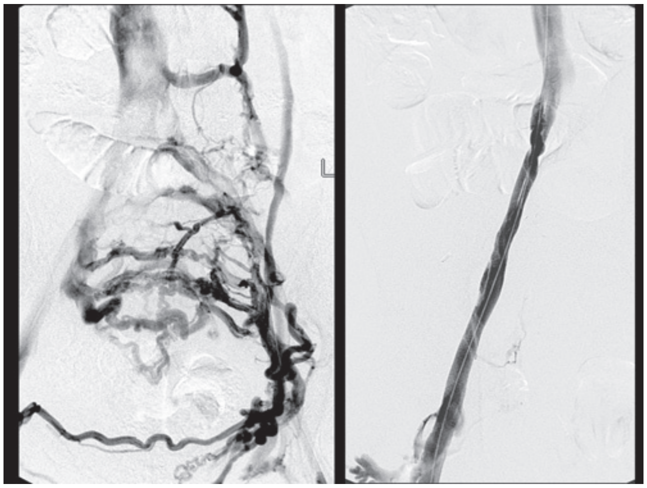


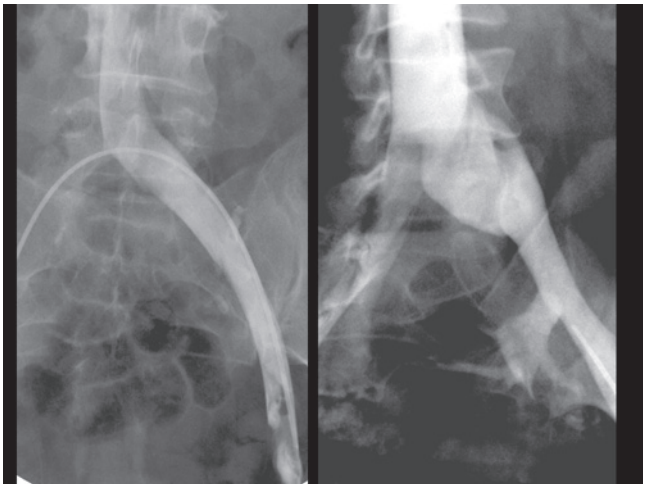
FIGURE 59.1 Transfemoral ascending venograms. (left) The typical image of a chronically occluded postthrombotic vein with axial and transpelvic collaterals. (right) A less frequently seen extensive iliac vein narrowing, a so-called Rokitansky stenosis, with a post-thrombotic perivenous fibrotic cylinder, which impedes any collateral development and expansion of the vein.

NONTHROMBOTIC, NONMALIGNANT, PRIMARY OBSTRUCTION

It is increasingly recognized that primary obstruction (iliac compression–type lesions) may be more important in the expression of nonthrombotic CVD than previously thought.[3] A so-called primary, nonthrombotic iliac vein obstruction (May-Thurner syndrome,[20] or Cockett's or iliac vein compression syndrome[21]) has been described. Typically, a stenosis of the left proximal common iliac vein is caused by compression by the right common iliac artery with secondary band or web formation (Figs. 59.2A–B).[9] The prevailing concept is that this syndrome is only clinically expressed in the left lower extremity of predominantly young women of child-bearing age. This limitation is not true since compression lesions are not uncommon in males, in elderly patients, and may involve the right limb. In our experience of treating iliofemoral obstruction in 938 limbs in 879 patients, 53% of limbs had nonthrombotic compression lesions (defined as absent history of DVT, no venographic or ultrasound findings indicating previous DVT), 40% had postthrombotic obstruction, and 7% had a combined etiology. The ages of the patients with nonthrombotic blockage ranged from 18 to 90 years (median 54 years), 20% of patients were men, and 25% of the symptomatic lower limbs were on right side.

INTRALUMINAL LESIONS

The important relationship of iliac vein compression lesions to the preponderance of left iliofemoral thrombosis was early recognized. Virchow attributed the marked left-sided predilection for deep venous thrombosis to stasis caused by compression of the left iliac vein by the right iliac artery against the fifth lumbar vertebral body.[22] *Iliac vein compression syndrome* is a misleading nomenclature since the lesion is not only characterized by narrowing due to



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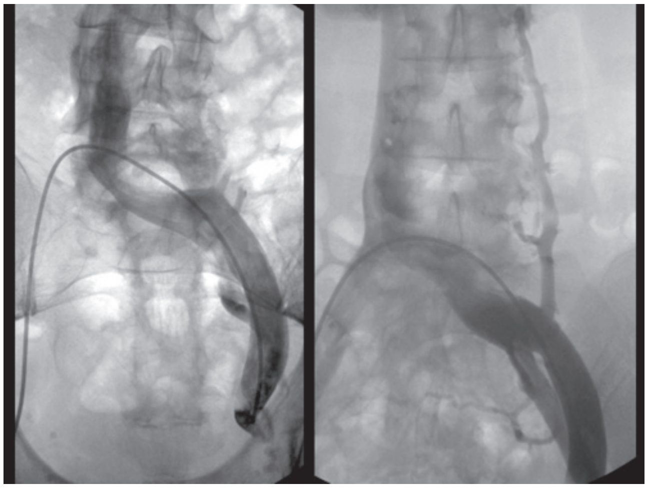

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FIGURE 59.2 **A**. Transfemoral ascending venograms. (left) A normal venogram showing a smooth continuously widening iliofemoral outflow tract. (right) Common iliac vein compression with severe flattening, "pancaking," in the frontal plane. A web is shown in the compression and collaterals are present. **B**. Transfemoral ascending venograms. (left) The stenosis of the left iliac vein due to compression by the right iliac artery is obvious. (right) Subtle thinning of contrast dye in the common iliac vein, "translucency," is suggestive of iliac vein compression. The filling of the ascending lumbar vein and transpelvic collaterals is suggestive of hemodynamically significant obstruction.

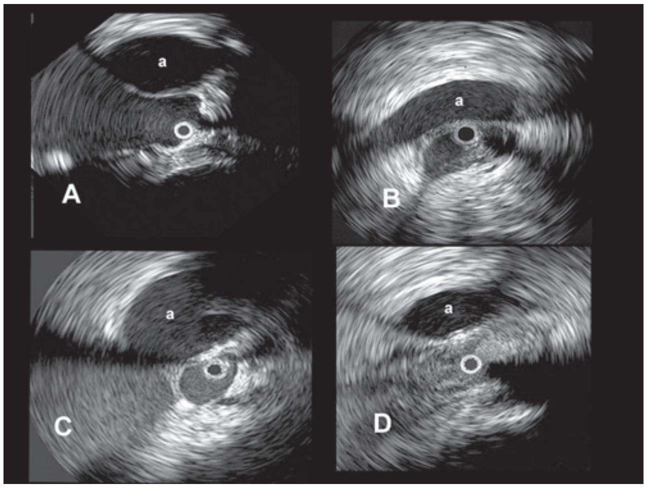

FIGURE 59.3 Images obtained by intravascular ultrasound (IVUS) at the site of an iliac vein compression. **A**. The right iliac artery crosses anterior to the left iliac vein, in this case creating moderate degree of compression. **B**. Compression of the iliac vein with an intraluminal web formation. **C**. A distinct septa underlying the compressing artery deforming and dividing the iliac venous lumen. **D**. Acute thrombosis of the compressed venous segment. The black circle inside the vein represents the inserted IVUS catheter (the a marks the right common iliac artery).

external compression, but also frequently by presence of intraluminal lesions acting as a weir in the bloodstream (Fig. 59.3). The nature of these lesions was described by McMurrich in 1908 to be an "adhesion" resulting in "fusion of the anterior and posterior wall of the vein." He thought the lesion was congenital and was surprised by its frequency (33%) in 107 unselected cadavers.[23] Ehrich and Krumbhaar confirmed the high prevalence of these obstructive intraluminal lesions (30% in 412 unselected autopsies) although they contested the etiology to be congenital.[24] These early studies lay dormant until interest was revived by detailed studies by May and Thurner in 1957.[20] They found a 22% incidence of iliac intraluminal lesions in 430 unselected cadavers. The morphology of the lesion varied from a thin membrane to "ridges, velums, chords, spurs or bridges" to total occlusion. Interestingly, the anatomist DiDio had already described these lesion in his doctoral thesis in 1949 and also introduced the concept of "venous spur" (personal communication by Alberto Caggiati). May and Thurner also discounted a congenital etiology and suggested that the predominant fibroblastic content of the lesion resulted from a proliferation of cells originating from the endothelium in response to chronic injury by the pulsating artery. Operating on these obstructions, Wanke earlier had observed a cicatricial sclerotic transformation of the common sheath secondary to iterative trauma and perivenous inflammation.[25] Arteriosclerotic inflammation of the artery at the vessel crossing also may affect the underlying vein and explain the finding of venous obstruction in elderly people. Increased incidence in women has been attributed to compression by the gravid uterus or increased lordosis. In the 1960s, Cockett et al. confirmed the high prevalence of the compressive iliac lesion in the general population (eight out of nine corrosion casts of the vein [88%] showed at least some degree of external compression) and 14% of 100 unselected cadavers had intraluminal lesions.[17,21]

Although the theory of congential etiology is not prevailing, there is some support for it. The presence of muscle, elastin, and collagen has been described in these lesions in

a layered structure, which would suggest an ontogenic, not traumatic origin.[9,24] The arterial crossover points also coincide with embryonic venous fusion sites where congenital webs and membranes may be present.[26] These occur more commonly on the left side. A post-thrombotic etiology of the intraluminal lesions appears to be ruled out due to the absence of hemosiderin and other features of an organizing thrombus, even though secondary thrombosis at the site or distally often is associated.[9,20] The etiology of these intraluminal lesions has not been proven convincingly.

ANATOMICAL CONSIDERATIONS

The exploration of iliofemoral veins with intravascular ultrasound (IVUS) has given new information regarding the iliac compression lesions. Although usually found in the common iliac vein, at least 15% of the limbs with primary disease have stenosis of both common and external iliac veins.[27] The anatomical differences between the right and left pelvic vasculature may explain the variable distribution of proximal and distal obstructive lesions.[9] The level of aortic bifurcation is variable, which affects relevant left-side anatomy very little, but has a major effect on artery/vein course relationships on the right side. The right iliac artery always crosses the left common iliac vein abruptly with the level of crossing showing minor variations (proximal left lesion). On the right side, the right iliac artery crosses the right common iliac vein only in 22% of cadavers coursing lazily across the vein over a longer length (proximal right lesion) (Fig. 59.4). In three-quarters of limbs, the right iliac artery crosses the right common iliac vein somewhat more abruptly low down at internal-external iliac vein junction (distal right lesion). In most cases, the right internal iliac artery does not cross the common or external iliac veins, because it originates before the iliac artery crossed the vein. The left internal iliac artery always crosses abruptly across the left iliac vein (distal left lesion) (Fig. 59.5). These anatomical variations may explain the greater frequency of proximal left compression lesions, the focal stenosis on the left and the diffuse lesion on the right side, and the same frequency of the distal lesions occurring bilaterally.

The possibility that these limbs with primary, nonthrombotic disease may have had an isolated subclinical iliac vein thrombosis that initiated at the vessel crossing and then propagated distally into the external iliac vein cannot be excluded. On the other hand, limbs with obvious post-thrombotic disease may have had an underlying iliac vein compression resulting in an iliofemoral vein thrombosis.[17,28] Whatever the chain of events, it serves to remind us that patients complaining of leg pain and swelling and no history

FIGURE 59.4 Transfemoral ascending venograms. (left) Distal iliac vein compression of the proximal external iliac vein in the sagittal plane (see also Figure 59.5). (middle) Long compression by the right iliac artery gradually transversing the right external iliac vein. (right) Left common iliac vein in a 76-year-old woman flattened by the arteriosclerotic artery, which is outlined by its calcifications.

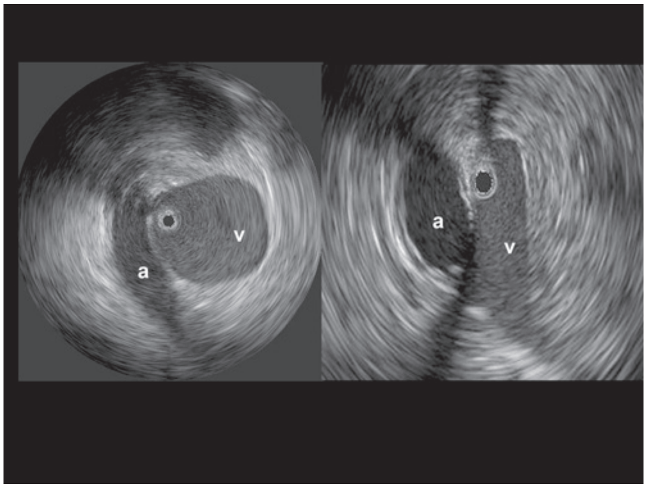

FIGURE 59.5 Images obtained by intravascular ultrasound (IVUS). The internal iliac artery (a) is seen crossing the external iliac vein (v) entering the pelvis. (left) No compression of the vein. (right) Significant compression of the vein, a distal compression lesion.

of previous DVT or other venous disease may have isolated iliac vein obstruction.

MISCELLANEOUS ETIOLOGY

Less common causes of chronic blockage of the iliac-caval vein include benign or malignant tumors, retroperitoneal fibrosis, iatrogenic injury, irradiation, cysts, and aneurysms. Relief of symptoms is immediate following successful stenting of malignant obstructions. The long-term outcome appears to depend largely on the progress of the tumor.[29] Iliocaval stenosis due to retroperitoneal fibrosis has been treated successfully by stenting.[30]

DIAGNOSIS OF VENOUS OBSTRUCTION

Often when algorithms are constructed for workup of patients with chronic venous insufficiency, investigations for estimating the degree of reflux are emphasized, and testing for outflow obstruction is omitted completely. This is mainly owing to a lack of accurate objective noninvasive or invasive tests for evaluation of hemodynamically significant chronic venous obstruction. There are many tests for delineating focal and global reflux, but this is not so for outflow obstruction.

There is no gold standard for assessment of venous obstruction. Unfortunately, it is not even known at what degree a venous obstruction is hemodynamically significant. The concept of a significant obstruction being a stenosis of >70–80% is derived from observations on the arterial system. There are many fundamental differences between the venous and arterial systems and it is certain that observations made on the arterial circulation are not necessarily transferable to the venous system. The effects of the venous obstruction are upstream (lack of emptying) rather than downstream (lack of perfusion), resulting in a different set of signs and symptoms. An arterial stenosis is first hemodynamically significant when it exceeds the high level of the peripheral resistance downstream. The iliac vein stenosis has only to override a low central resistance, so a significant stenosis may be at a much lesser degree than 70%. The development of arterial collaterals may improve distal arterial perfusion but venous collaterals appear to poorly replace inadequate outflow due to its meandering course and valve orientation.[31]

The venous circulation is a low pressure, low velocity, and large volume vascular system as compared to the high pressure, high velocity, and small volume arterial system. It is important to remember that in such a system, the venous pressure is a function of not only resistance to the flow (degree of obstruction and collateral formation), but also depends to a higher degree on the flow velocity and magnitude of volume flow. Only small pressure differences at rest may indicate significant obstruction. The contralateral veins converge beyond the iliac stenosis, which may mitigate any IVC to femoral vein pressure gradient at rest. At present, the accepted view is that a significant obstruction exists with a supine pull-through gradient greater than 2 to 3 mmHg at rest, or with a gradient compared to the contralateral femoral pressure exceeds 2 to 5 mmHg as measured in supine position. The prevailing rule is that femoral venous pressure increase on exercise should be at least 5 mmHg to warrant intervention. These pressure differences are certainly much lower than in the arterial system, and may be difficult to measure accurately.[32–34] These suggested pressure levels to detect significance are set arbitrarily. In a supine position, especially during surgery, it is difficult to increase the venous outflow sufficiently to detect a borderline hemodynamic obstruction. Although a positive hemodynamic test may indicate hemodynamic significance, a normal test does not exclude it. So, in fact, it is not known at what degree a venous stenosis should be considered hemodynamically critical.

Ultrasound investigation and outflow fraction determinations by plethysmographic methods have been shown to be unreliable and play only a limited role. Although abnormal plethysmography findings may indicate obstruction to the venous outflow, significant blockage may exist in the presence of normal findings.[35–37] Even the invasive pressures (i.e., hand/foot pressure differential and reactive hyperemia pressure) increase, and indirect resistance calculations appear insensitive and do not define the level of obstruction.[37] Unfortunately, it is presently impossible to detect borderline obstructions, which may be of hemodynamic importance.

ROLE OF TRANSFEMORAL VENOGRAM

Since accurate hemodynamic tests are unavailable, diagnosis and treatment must be based on morphological findings. New promising noninvasive morphological tests with spiral CT and MRV are under evaluation, but their role in the workup of venous obstruction is not yet defined. Still the single-plane transfemoral venogram is the standard investigation and may show definite obstruction and development of collaterals. Although a defined lesion may be obvious, findings on the anterio-posterior (AP) view are often subtle and only suggestive of an underlying obstruction; for example, widening of the iliac vein (pancaking), thinning of the contrast dye resulting in a translucence of the area, partial intraluminal defect (septum), or a minimal filling of transpelvic collaterals (Figs. 59.2A-B). Increased accuracy may be achieved with multiple angled projections, which may reveal surprisingly tight stenosis on oblique projections, although the AP view is quite normal (Fig. 59.6).[38] The hemodynamic impact of this stenosis is not known from morphologic studies. As pointed out previously, the compensatory role of collateral formation is doubtful since blood flow through these meandering vessels hardly can replace the flow through the straighter main vein. The collaterals observed pre-stent often disappear promptly following stenting of a significant stenosis. The flow through the stent is obviously favored. The presence of collaterals in a symptomatic patient perhaps should be considered an indicator of obstruction.

ROLE OF INTRAVASCULAR ULTRASOUND (IVUS)

IVUS can detect only axial collaterals running close to the original vessel. Transpelvic collaterals will escape detection. Several studies have shown, however, that IVUS is superior to the single-plane venography in detection of the extent and morphologic degree of stenosis.[8,35,39,40] IVUS shows intraluminal details (e.g., trabeculations and webs) that may be hidden in the injected contrast dye (Fig. 59.7). An external compression with the resulting deformity of the venous lumen can be directly visualized, and wall thickness, neointimal hyperplasia, and movement can be seen. Most importantly, IVUS appears superior to standard single-plane venography for estimating the morphological degree of iliac vein stenosis. On average, the transfemoral venogram significantly underestimated the degree of stenosis by 30%. The venogram actually was considered normal in one-fourth of limbs despite the fact that IVUS showed >50% obstruction.[27] Interestingly, Cockett and colleagues made similar observations. Venography was diagnostic in only 65% of obstructed limbs in their material, and collaterals were visualized only in 63%. It was noted that in 54% of symptomatic patients, transfemoral venography appeared normal with smooth contours of contrast in the iliac vein and without collaterals. The authors noted that absence of collateral formation should not negate consideration of the pathology.[9,17,21]

IVUS is clearly superior to single-plane venography in providing adequate morphological information and is pres-

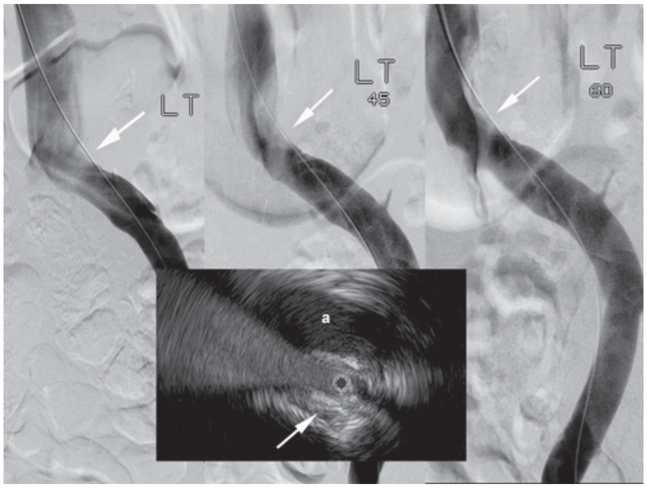

FIGURE 59.6 Transfemoral venogram and IVUS image of a focal stenosis of the left iliac vein (arrow). The 45º and 60º oblique films delineate the stenosis better than the AP view. The IVUS image is conclusive. The adjacent artery is marked with an a. The black circle within the vein is the IVUS catheter.

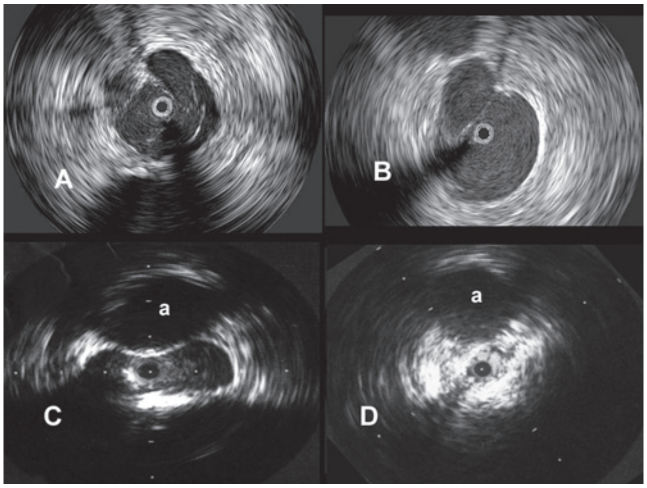

FIGURE 59.7 Images obtained by venous intravascular ultrasound (IVUS). **A**. Trabeculation with multiple lumina. **B**. Intraluminal septa. **C**. Moderate compression by the artery of a thin-walled vein. **D**. Severely compressed vein with sclerotic thick wall. The black circle inside the vein represents the inserted IVUS catheter and the a marks the artery.

ently the best available method for diagnosing clinically significant chronic iliac vein obstruction.

PRACTICAL IMPLICATIONS

There are no reliable tests to measure a hemodynamically significant stenosis. This lack of gold standard is the major obstacle to assess the importance of chronic outflow obstruction, select limbs for treatment, and evaluate the outcome. Although a positive noninvasive or invasive test may support further studies, a negative test should not exclude it. The diagnosis and treatment must presently be based on invasive morphological investigations of the iliac venous outflow (transfemoral multiplane venography or IVUS), or perhaps in the future MRV or spiral CT. Limiting workup of patients with significant chronic venous disease to only duplex ultrasound will not suffice. The key for the physician is to be aware of the importance and possibility of venous blockage combined with increased suspicion in patients with history and clinical signs and symptoms suggestive of outflow obstruction. Patients with previous DVT; patients with limb symptoms, especially pain, out of proportion to detectable pathology; patients not improving on conservative treatment; and patients with no other detectable pathology explaining their symptoms are specifically targeted.

In selecting patients for IVUS investigation, the following indicators of obstruction have been used: 1) venographic stenosis >30%; 2) presence of pelvic collaterals; and 3) positive invasive pressure test.[27,39,41] IVUS may be performed when one or several of these indicators are present and the patient is symptomatic. Utilizing this policy, however, 10 to 15% of iliofemoral veins are found to be normal.

Arbitrarily, we consider to stent limbs with ilio-caval vein stenosis with more than 50% reduction of the luminal cross-cut area as measured by IVUS, especially if pre- or intraoperative pressure gradients indicate hemodynamic significance. Intraoperative pressure changes are not decisive to allow stenting, but increased venous pressure levels support the intervention.

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C H A P T E R

60

Treatment of Iliac Venous Obstruction in Chronic Venous Disease

PETER NEGLÉN

The previous chapter has outlined the etiology and diagnosis of obstruction in the iliofemoral venous outflow tract. Until a decade ago open venous bypass surgery was the only available intervention. It was unattractive for several reasons and restricted to a minority of patients with severe disabling symptoms. The introduction of endovascular treatment with percutaneous stenting drastically changed the treatment and view on venous outflow obstruction. Iliac venous stenting has already largely replaced surgery as the "method of choice" for treatment of venous blockage. The relative simplicity, safety, and efficacy of the intervention has refocused the interest on the role of venous outflow obstruction in patients with chronic venous disorders, and has renewed interest in the nature and pathophysiology of venous obstruction in itself and in tests for detection of hemodynamically significant lesions. However, venous stenting is still under development, and there are several issues regarding diagnosis, assessment of outcome, and selection of patients, which needs to be resolved.

OPEN SURGICAL RECONSTRUCTION

Open surgical bypasses can be performed to alleviate severe venous outflow obstruction. The operations most frequently used are femoro-femoral crossover or unilateral ilio-caval bypass for proximal iliofemoral vein occlusion. Reconstruction with sapheno-popliteal bypass for distal femoro-popliteal obstruction is today of historical note only. Right iliac artery transposition and iliac vein patch angioplasty have been used in selected patients with focal iliac vein compression syndrome, but are now abandoned.[47] The open operation constitutes major surgery and to keep it patent it often is combined with temporary or permanent arteriovenous fistula and life-long anticoagulation with inherent risk of complications. Strict criteria for surgery, including severe disabling symptoms and markedly increased venous pressure levels, are used and only a minority of patients with chronic venous disease (CVD) are selected.

The outcome of open surgery has not been so convincing as to make a major impact on the routine treatment outflow obstruction and has been limited to a selective group of patients with the most severe clinical condition. The results following open reconstructions usually are presented in series with small numbers of treated limbs and rarely are cumulative patency and success rates given. The general problem with bypass grafting is relatively poor long-term patency. The reasons for this are several. The grafts tend to clot because the area of insertion has low velocity flow, external compression of the low pressure bypass may occur, nonsaphenous graft material is inherently thrombogenetic, and the distal inflow is often poor due to extensive distal disease. The saphenous vein must be unaffected by any disease in order to be utilized. Inadequate size, phlebitic obstruction, or valve incompetence are factors often precluding the use of the autogenous vein. Best result with in-line bypasses has been achieved with large-diameter PTFE graft (10 mm) with external support (ringed), adjunct use of an arteriovenous fistulae, and meticulous perioperative anticoagulation.[10,24] The arteriovenous fistula is left in place and anticoagulation continued as long as no side effects occur and the bypass stays patent. Lifelong anticoagulation is usually necessary to keep the bypass open. If the graft suddenly occludes with a functioning fistula, symptoms of pain and swelling are accentuated and the fistula has to be disconnected.

THE CROSS-OVER BYPASS

The cross-over bypass can be constructed either by using the contralateral saphenous vein or a prosthetic graft (Figure 60.1). The donor vein is exposed and then rotated at the saphenofemoral junction to cross to the other side (classic Palma technique[39]) or used as a free femoro-femoral graft. This free saphenous graft appears to do better than rotation of the vein avoiding kinking at the saphenofemoral junction.[9] The autogenous cross-femoral venous bypass appears to be less thrombogenetic with better cumulative patency rate than prosthetic grafts (at 2 years, 83% and 54%, respectively).[21] The cross-over reconstruction has been reported to be durable with good symptom relief, so called "clinical" and venographic patency ranging from 44 to 100% with a follow-up of five years.[1,7,9,12–14,18,19,21,36,50] Most series have small numbers of patients with inconsistent clinical and venographic follow-up (see Tables 60.1 and 60.2).

Halliday et al. performed the only cumulative analysis existing showing a 75% cumulative venographic patency rate at five years.[14] This excellent result has not been reproduced elsewhere. Clinical improvement is unfortunately not necessarily related to graft patency. Superior results are achieved if the inflow channel is normal. Despite remaining patent the saphenous grafts may give poor symptom relief owing to its small cross-cut area and relatively large resistance to flow. It has been shown that at least a 4.0 mm diameter vein is necessary to adequately relieve the iliac vein outflow obstruction.[24] This is the reason for recommended size of a 10 mm PTFE graft for femoral cross-over bypass as an alternative to the absence or an inadequate size of the saphenous vein.

TABLE 60.1 Results of Saphenous Vein Femoro-Femoral Bypass

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husni[18]	78	7–144	74	73
Hutschenreiter et al.[19]	20	6–28	69	44
O'Donnell et al.[36]	6	24	100	100
Halliday et al.[14]	47	60	89	75
AbuRahma et al.[1]	24	66	88	75

TABLE 60.2 Results of Prosthetic Femoro-Femoral Bypass

Author	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Eklof et al.[10]	7	2–31	86	17
Yamamoto et al.[50]	5	1–18	60	60
Comerota et al.[7]	3	40–60	67	67
Gruss and Hiemer[13]	32		85	85

THE IN-LINE BYPASS

Anatomic in-line bypass reconstruction can be used in the femoro-ilio-caval axial outflow axis with segmental obstruction in the presence of a sufficient venous in- and outflow of the graft. Most frequently a PTFE-graft is used, but spiral saphenous graft may also be used, if available. As with cross-over bypasses, the in-line reconstructions, especially when starting in the groins, are constructed with a concomitant arteriovenous fistula, and lifelong anticoagulation is usually necessary for patency. Patency rates during follow-up from one to 150 months vary from 29 to 100% (see Table 60.3).[2,8,11,17,20,38,41]

The only cumulative study by Jost et al. shows a secondary patency rate of 54% at two years for prosthetic in-line bypass.[21] This should be compared to 83% for saphenous vein femoro-femoral cross-over bypass in the same study. Early patency for caval reconstruction with excision of the cava and interposition graft for malignant disease is better than in-line bypasses for postthrombotic obstruction.[5]

STENTING OF THE ILIO-FEMORAL VEIN

Venous stenting has been used to successfully treat iliac vein obstruction of various etiologies such as postthrombotic occlusion, iliac vein compression syndrome, and malignant obstruction (Figures 60.2 and 60.3). The complication rate related to the endovascular intervention is minimal

TABLE 60.3 Results of Femoro-Caval/Ilio-Caval Prosthetic Bypass Grafting

	Number of limbs	Duration of follow-up, months	Clinical success, %	Patency, %
Husfeldt[17]	4	4–30	100	100
Dale et al.[8]	3	1–30	100	100
Ijima et al.[20]	5	22–36	60	60
Eklof et al.[10]	7	2–31	86	29
Plate et al.[41]	3	1–11	67	33
Okadome et al.[38]	4	17–48	100	100
Gloviczki et al.[11]	12	1–60	67	58
Alimi et al.[2]	8	10–45	88	88
Jost et al.[21]	13	1–150	49	54

and comprises mostly cannulation site hematoma. A minimal number of acquired arteriovenous fistulas when the cannulation site is distal on the thigh have been observed, and a few cases of retroperitoneal hematoma requiring blood transfusions have been described.[16,34] The utilization of ultrasound-guided cannulation and closure of the cannulation site with collagen plugs largely have abolished these problems. The mortality has been nil.

Studies of venous stenting in peer review publications have often similar shortcomings as reports for open surgery. Most studies are case reports and few are sizable; the follow-up is short-term, and patency not reported in cumulative fashion, stented sites in the upper and lower extremities are mixed, and the majority of the reports' series have not differentiated between etiologies or in management of acute and chronic conditions.

An unveiled proximal chronic obstruction of the iliac vein following thrombectomy or lysis is known to decrease future patency if not treated. Stenting of the stenosis after clot removal will improve iliofemoral patency from 27 to 44%, to 86 to 93%.[23,29,49] It appears that the patency rates after stent placement following immediate removal of acute thrombosis and in treatment of chronic postthrombotic disease are similar. It also has been shown that limbs treated with ilio-caval stent placement after lysis of acute deep vein thrombosis have a greater one-year patency as compared to limbs undergoing only balloon angioplasty (74 and 53%, respectively).[28]

Successful stenting of malignant lesions are gratifying since relief of symptoms is immediate. The long-term outcome appears to depend largely upon the progress of the tumor rather than stent properties per se.[6]

STENT PATENCY OF MIXED-ETIOLOGY GROUPS

There are several smaller studies of iliofemoral stenting for mixed patient groups of different etiology and with or without adjuvant surgical thrombectomy or lytic clot removal. Most results are not analyzed cumulatively a.m. Kaplan-Meier. These studies are summarized in Table 60.4. Nazarian et al. found in such a mixed-etiology group of patients that only a few occlusions occurred after six months and that the patency rate remained the same at one- and four-year follow-up.[30] Lamont et al. presented cumulative result. After stent insertion in 15 limbs (9 following acute DVT removal), a cumulative secondary patency rate of 87% at 41 months as measured by duplex ultrasound was achieved.[25]

STENTING OF CHRONIC NONMALIGNANT OBSTRUCTION

A few studies describe stenting of nonmalignant chronic obstruction with no adjuvant therapy in patients with chronic venous disease. Blättler and Blättler reported in 1999 treatment of chronic venous and neurogenic claudication due to pelvic venous blockage and achieved 100% patency in 11 successfully stented limbs with a mean follow-up of 15 months (range 1–43 months).[4] A group of 18 patients were reported by Hurst et al.[16] Twelve limbs were treated for chronic obstruction. The primary patency rates at 12 and 18 months were 79% and 79%, respectively. Hartung et al. has reported the result after stenting of 44 patients with

TABLE 60.4 Patency Rates Following Femoro-Ilio-Caval Stenting of Patients with Mixed Etiology and Varying Adjuvant Treatment

Author	Number of limbs	Etiology and adjuvant treatment	Duration of f/u	Patency rate: Primary	Assisted	Secondary
Nazarian et al., 1996[30]	56	Mixed	4 years (cumulative)	50%		75%
Binkert et al., 1998[3]	8	With and without thrombectomy	10–121 months	100%		
O'Sullivan et al., 2000[37]	34	With and without thrombolysis	1 year	79%		
Patel et al., 2000[40]	10	After thrombolysis	6–36 months	60%		100%
Hurst et al., 2001[16]	18	With and without thrombolysis	1.5 years	79%		
Juhan et al., 2001[22]	15	With and without thrombectomy	5–52 months	87%		93%
Lamont et al., 2002[25]	15	With and without thrombectomy	41 months (cumulative)			87%
Schwarzbach et al., 2005[45]	20	With thrombectomy and lysis	0.5–77	80%		90%
Delis et al., 2004 (Personal communication)	41	With and without thrombolysis/ectomy	6 months	58%	71%	76%

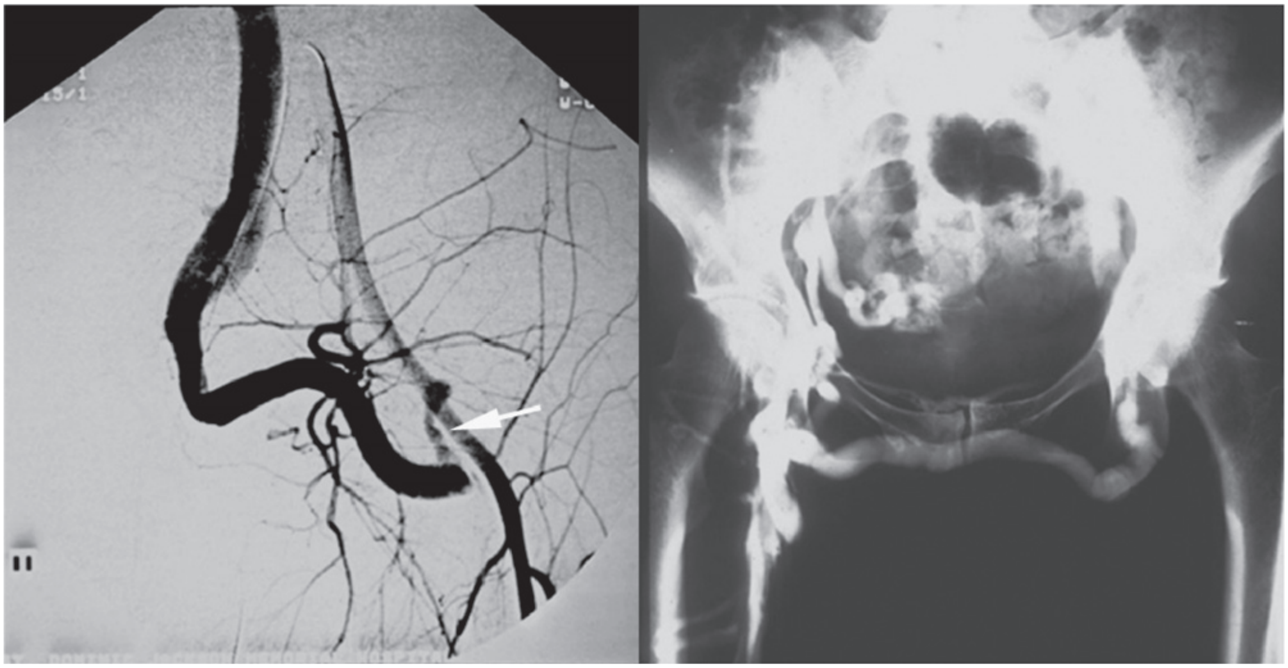


FIGURE 60.1 (Left) Contrast dye injected in the left iliac artery visualizes a ringed PTFE femoro-iliac left-to-right bypass graft through the intentionally created arteriovenous fistula (arrow). (Right) An ascending venogram fills an autogenous vein femoral cross-over bypass of adequate size (Palma procedure).

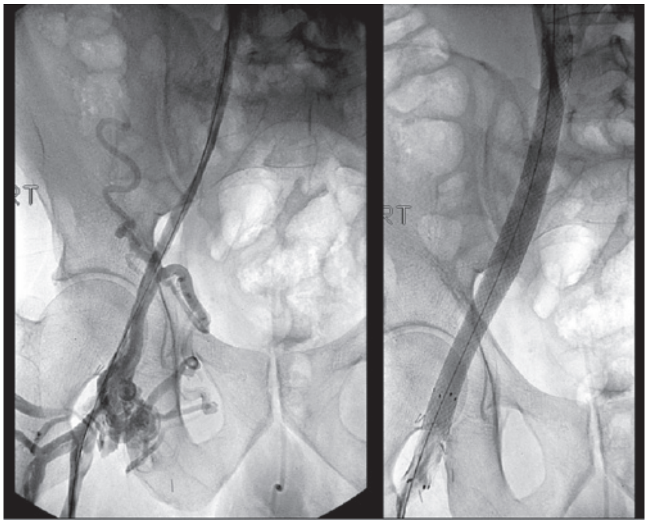


FIGURE 60.2 (Left) Venogram following recanalization of chronic postthrombotic obstruction of the right iliofemoral vein after passage of a guidewire and initial balloon angioplasty with small-diameter balloon. (Right) Note the disappearance of collaterals on repeat venogram after further dilation and stenting have ensured an excellent outflow by overlapping multiple stents covering the entire left iliofemoral vein.

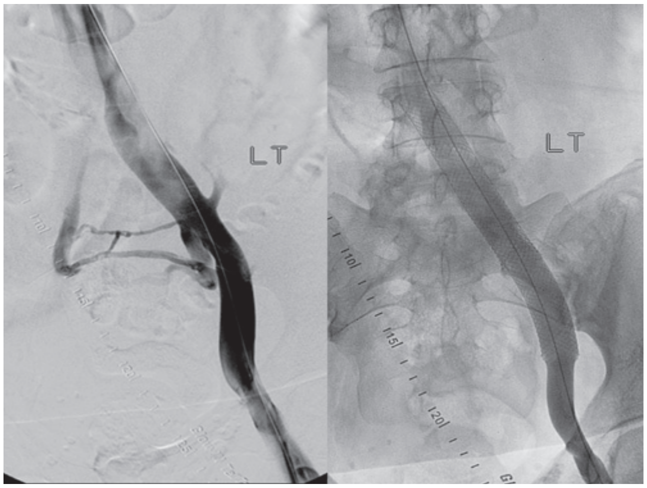


FIGURE 60.3 Intraoperative transfemoral venogram before (left) and after (right) balloon dilation and insertion of two overlapping stents in a patient with nonthrombotic disease (iliac vein compression syndrome). The prestent translucent common iliac vein and presence of collaterals, despite poorly defined stenosis, are typical findings. The collaterals most often do not fill on repeat venogram after adequate stenting.

chronic disabling ilio-caval obstruction. Cumulative primary, assisted-primary, and secondary patency rates were 73, 88, and 90% at 36 months.[15]

Several reports have been published by our group describing results after stenting of pelvic and caval veins in patients with chronic nonmalignant occlusions without any pretreatment of acute deep vein thrombosis.[31,33,34,43,44] Cumulative patency rates based on venographic findings as defined by reporting standards of SVS/ISCVS,[42] frequency of in-stent recurrent stenosis, clinical results assessing pain, swelling and ulcer healing, and limited quality-of-life data are avail-

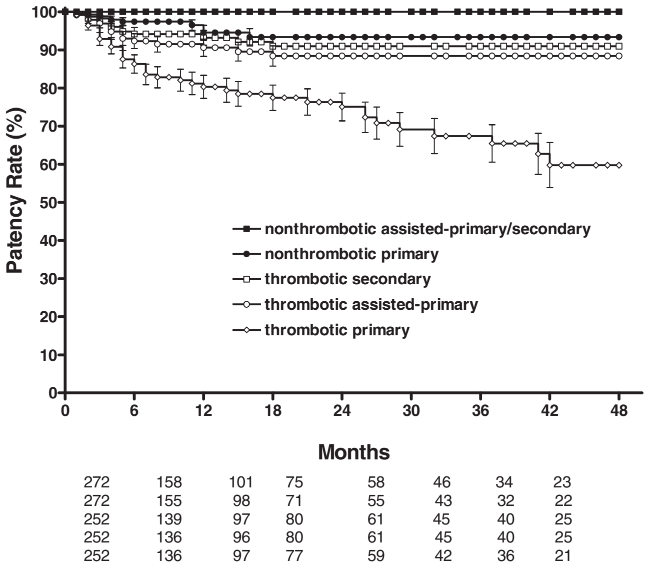


FIGURE 60.4 Cumulative primary, assisted-primary, and secondary patency rates for stented limbs with thrombotic and nonthrombotic obstruction. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

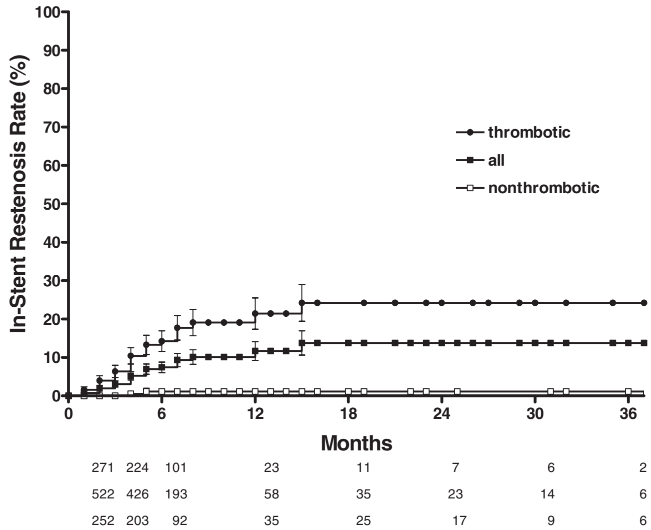


FIGURE 60.6 Cumulative in-stent restenosis rate (stenosis >50%) in all stented limbs. The higher restenosis rate is obvious in thrombotic as compared with nonthrombotic limbs. The numbers below the graph represent total limbs at risk for each time interval (all SEM <10%).

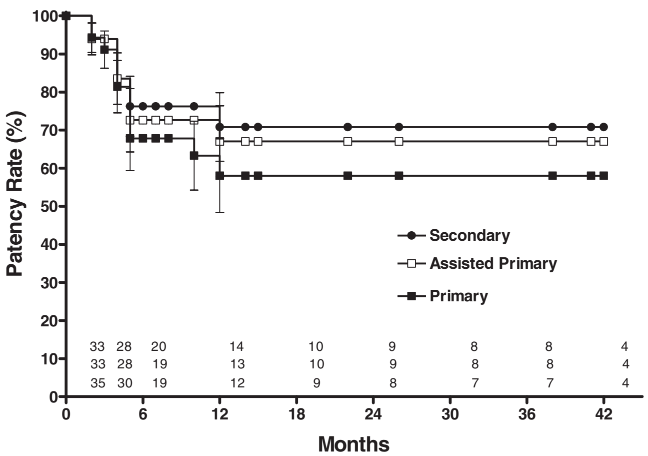


FIGURE 60.5 Cumulative primary, assisted-primary, and secondary patency rates for severely diseased postthrombotic limbs with outflow occlusion, which require guidewire recanalization and sequential balloon venoplasty before stent placement. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

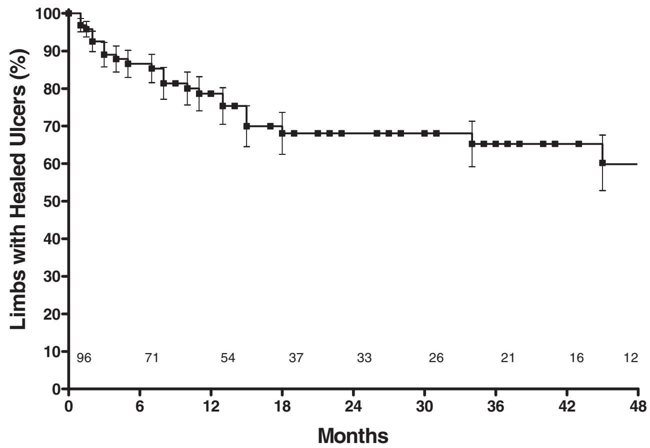


FIGURE 60.7 Cumulative rate of limbs with no recurrence after initial healing of leg ulcer. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

able. The obstructive lesion in these reports was considered post-thrombotic when the patient had a known history of DVT or when post-thrombotic changes was found on venography or ultrasound at any level of the lower extremity. The remaining limbs were considered nonthrombotic (primary). No obstructions due to malignancy were included.

The published material[31,35,34] recently has been updated and the most recent results are given here. There is no alteration of the basic material but merely a longer follow-up. The results appear to be remarkably stable even with longer follow-up. One or several transfemoral venograms were performed after treatment in 565/789 limbs, which underwent iliac vein stenting between 1997 and 2004. Cumulative primary, assisted-primary, and secondary patency rates at five years were 75, 94, and 96%, respectively. The stented limbs with nonthrombotic disease appeared to fare significantly better than did those with thrombotic disease (primary, assisted-primary, and secondary cumulative patency rates of 94, 100, and 100%, and 60, 88, and 91% at 36 months, respectively) (Figure 60.4). The lowest patency rates were seen in 35 patients with long occlusions, which had to be bluntly recanalized and sequentially dilated before stenting

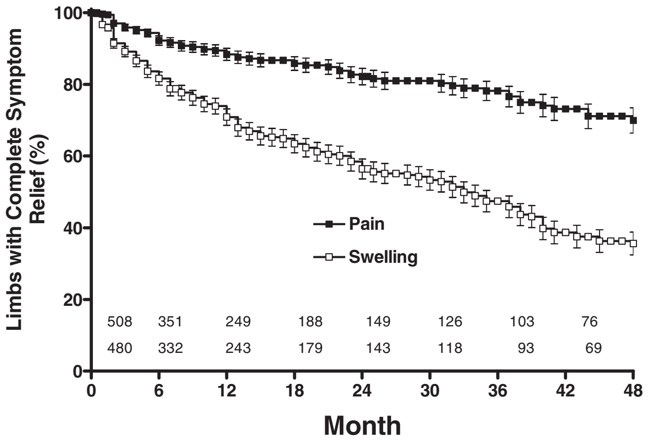


FIGURE 60.8 After venous stenting a substantial number of patients become free of pain and swelling. This graph shows the cumulative rate of limbs with maintained complete relief of swelling and pain during four years after intervention. The lower numbers represent total limbs at risk for each time interval (all SEM <10%).

was possible (primary and secondary patency rates at 48 months, 58 and 71%, respectively) (Figure 60.5).

Although some degree of in-stent recurrent stenosis (ISR) is common (only 23% were completely free of any stenosis at 42 months)[35] severe in-stent recurrent stenosis, that is, >50% diameter decrease on single plane anterior-posterior venogram, is infrequent (only 13–14% present in 36–48 months) (Figure 60.6).[15,35] Several factors, which may potentially influence the development of ISR, were analyzed. Gender and sidedness of limb involvement did not affect outcome. Cumulative higher rates of severe IRS occurred with treatment of thrombotic than in nonthrombotic limbs (24 and 1%, respectively) at 48 months, and in the presence of thrombophilia (18 and 12%, respectively). The data concerning the length of stented area and extension of stent system to below the inguinal ligament appear intimately connected. Length of stented area 13–35 cm and extension of stent to below the inguinal ligament had a cumulative rate of severe ISR of 25% at 36 months and 40% at 24 months, respectively.

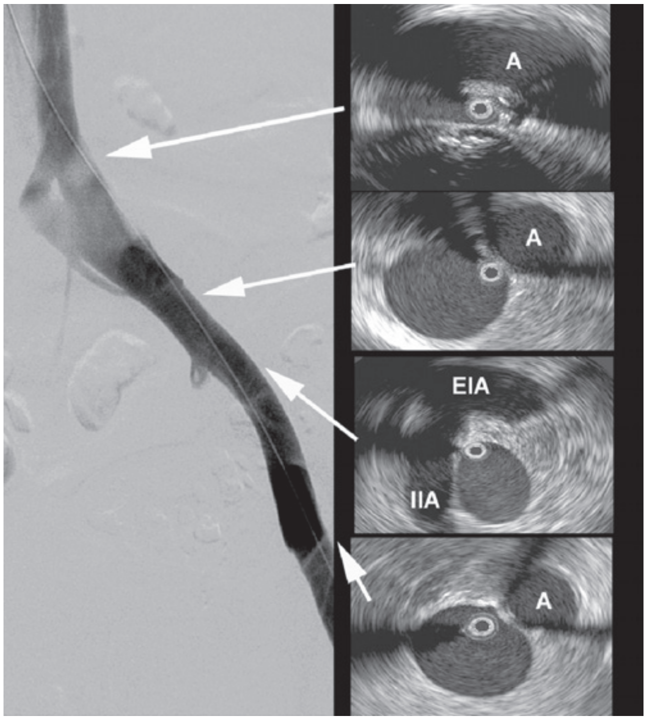
The strong impact of the thrombotic disease on development of in-stent restenosis appears to be reflected in the analysis of other potential contributing factors. There was an overrepresentation of limbs with thrombotic disease in patients with thrombophilia, long stents, and stents terminating below the inguinal ligament, which all had higher rates of in-stent restenosis. The result may reflect treatment of a more severe and extensive disease seen in limbs with thrombotic disease.

Although groups of limbs with multiple follow-up venograms do not unequivocally show an increase of stenosis over time, there is no doubt that there may be significant progress in individual cases. Whether the late occlusions occur due to acute recurrent thrombosis or gradual development of true intimal hyperplasia requires further study. The three major risk factors for development of ISR and late occlusion appear similar. At 24 months post-stenting, limbs with the three risk factors outlined earlier showed a 61% rate of severe in-stent restenosis, but none developed in the their absence. No conclusion regarding a cause-effect relationship can be drawn from this paper.[35]

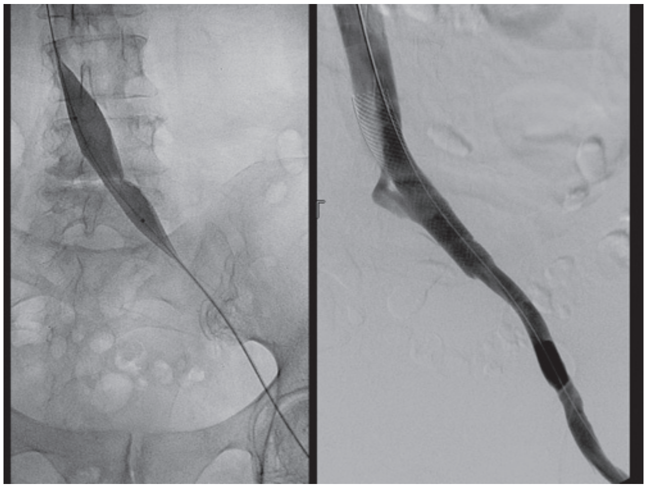
CLINICAL OUTCOME AFTER STENTING

The reports referred to earlier describing patency rates indicate clinical improvement in most patients (>80%).[3,4,37] Hurst et al. showed resolution or substantial improvement in 72% of limbs.[16] However, five remaining patients continued to have pain despite resolved swelling and widely patent stents on venogram. In addition to assessment of ulcer healing, Raju and Neglén have evaluated pain, swelling, and quality-of-life. Median follow-up 789/993 limbs in the updated material was 11 months (range: 1–88 months). The degree of swelling was assessed by physical examination (Grade 0: none; Grade 1: pitting, not obvious; Grade 2: ankle edema; Grade 3: obvious swelling involving the limb), the level of pain was measured by the visual analogue scale method,[46] and quality-of-life by a questionnaire, validated for assessment of chronic venous insufficiency.[26] The incidence of ulcer healing after iliac vein balloon dilation and stent placement in 41 limbs with active ulcer was 68% and the cumulative ulcer recurrence-free rate at two years was 62%.[44] The updated data show a cumulative freedom of ulcer recurrence of 60% at four years in 96 stented ulcerated limbs (Figure 60.7). During the observation period no additional surgery was performed to treat any concomitant reflux. Median swelling and pain severity scores decreased significantly (grade 2 to 1 and 4 to 0, respectively). The frequency of limbs with any swelling decreased significantly from 82 to 48% and limbs with any pain fell from 78 to 21% (updated result). The improvement of pain and swelling was significant in both ulcerated and nonulcerated limbs, indicating that the ulcer was not the only cause of pain and swelling. The cumulative rate of maintained relief of pain and swelling in patients who achieved complete pain and swelling relief after stenting was better in regard to pain as compared to swelling at 4.5 years (70% and 36%, respectively) (Figure 60.8).

Using a quality-of-life questionnaire assessing subjective pain, sleep disturbance, morale and social activities, routine and strenuous physical activities, the patients indicated significant improvement in all major categories after venous stenting.[44] Hartung et al. have shown a significant improvement of median venous clinical severity score (VCSS) and venous disability score (VDS) after stenting (8.5 [range: 4–18] and 2 [range: 0–9], present vs. 2 [range: 2–3] and 0 [range: 0–2] poststent, respectively).[15] The clinical outcome is favorable in the intermediate to long term. The results clearly indicate significant symptom relief after balloon



A



B

FIGURE 60.9 **A**. (Left) Prestent intraoperative transfemoral venogram showing a nonthrombotic lesion proximally with translucency of the common iliac vein. An axial collateral or an intraluminal septa is suggested. (Right) IVUS of the same vein at different levels shows severe proximal common iliac vein (CIV) stenosis due to compression by the crossing iliac artery and normal distal CIV (top images). There is no compression of the external iliac vein at the bifurcation of the iliac artery (internal iliac (IIA) and external iliac (EIA) arteries) (middle) and normal width of the external iliac vein (bottom). The adjacent artery is marked with an A. The black circle within the vein is the IVUS catheter.
B. The IVUS investigation clearly delineated the extent of the lesion, which was limited to the proximal common iliac vein (CIV). (Left) The balloon venoplasty is performed with obvious wasting of the balloon at the site of the stenosis. Because of immediate recoil, a stent is placed well into the IVC and distally covering the CIV. (Right) The repeat venogram shows no translucency but still filling of the axial collateral.

angioplasty and stent placement to treat iliac venous outflow obstruction.

ENDOVASCULAR TECHNIQUE

Balloon angioplasty with stenting of the venous system is minimally invasive and straightforward to perform, but attention to details is important to achieve satisfactory results. The detailed technique is described elsewhere.[33,34,37,43] Venous stenting is fundamentally a different procedure from stenting in the arterial system; for example, the "kissing" balloon technique at the confluence of the common iliac veins or insertion of bilateral stents is not necessary. Experience acquired with endovascular treatment of arterial obstructive disease cannot necessarily be transferred directly to the venous system.

The procedure may be performed under local infiltration analgesia in combination with monitored sedation or general anesthesia (Figure 60.9). Since the balloon dilation may be quite painful the latter is recommended when tight stenoses or occlusions are stented. Attempts to recanalize occluded veins are also often time consuming. The procedure should be performed in a fully equipped endovascular or angiographic suite and availability of IVUS and external ultrasound for cannulation guidance is preferred. The cannulation of the femoral vein under ultrasound guidance largely has eliminated access complications. There is no problem of hemostasis, even in the middle of the thigh, as would be encountered after arterial puncture. Ipsilateral cannulation of the femoral vein is obtained under ultrasound guidance below the suspected obstruction. Low thigh access is necessary in extensive obstruction to allow stent deployment up to and below the inguinal ligament without being impeded by the sheath. Popliteal vein access rarely is used and often not possible because of segmental occlusion of the post thrombotic femoral vein.

It has been shown previously that simple balloon dilation leads to early restenosis and an immediate recoil of the iliac vein has been observed intraoperatively in the majority of limbs.[27,32,48] The external pressure is usually severe and often focal. Contrary to the case with endovascular treatment of arterial obstruction, stenting is, therefore, advised in nearly all endovascular surgery to correct venous obstruction.

If a braided stent (e.g., Wallstent®) is used, it should be placed well into the IVC in stenosis closed to the confluence of the common iliac veins (Figure 60.9B). Owing to its inherent properties it is otherwise frequently displaced (squeezed) distally and a proximal restenosis may develop.[34] This IVC placement raises concern for risk of occlusion of the contralateral limb. The stent, however, does not appear to significantly impair the flow from the contralateral limb resulting in thrombosis. Only a few cases of contralateral limb DVT has been observed and appear to be caused by recurrent attacks of thrombosis.

Insertion of a self-expanding flexible large stent (14–16 mm diameter) is recommended. The vein seems to accept extensive dilation without clinical rupture contrary to the artery. No clinical rupture of the vein has been reported so far, even when a total occlusion is recanalized and dilated up to 16 mm width. Redilatation after stent insertion is mandatory to achieve a good wall apposition as evaluated by IVUS.

The intravascular ultrasound (IVUS) is valuable as a diagnostic tool, but it is vital as an intraoperative aid to direct placement of the stent (Figure 60.9A). It is essential to determine the extent of the lesion for appropriate placement of the stent. The diseased vein segment is frequently more extensive in reality than indicated by venography. The inflow and outflow of the stent cannot be impeded to ensure long-term patency. Therefore, it is vital to cover the entire obstruction as outlined by the IVUS. Unstented skip areas in between two stents should be avoided. When multiple stents are used, they need to substantially overlap to prevent separation. There should be no hesitation to extend the stent below the inguinal ligament if the lesion reaches the common femoral vein. The occlusion rate does not appear to be related to the length of stent or metal load per se, but to incomplete treatment or other factors.

The perioperative thrombosis prophylaxis is fairly standardized in all patients. The patient received 2500 units subcutaneously of dalteparin preoperatively. During the procedure, 5000 units of unfractionated heparin and 30 mg ketorolac were administered intravenously. All patients were admitted for less than 23 hours. Postoperatively, a foot compression device was applied, dalteparin 2500 units administered subcutaneously in the recovery room; and a ketorolac injection and dalteparin 5000 units repeated in the morning before discharge. Low dose aspirin (81 mg p.o.) daily was started immediately postoperatively and continued. Most patients did not have additional anticoagulation. Only patients already on warfarin preoperatively owing to prior recurrent deep vein thrombosis and/or thrombophilia or those with significant thrombophilia discovered preoperatively were anticoagulated postoperatively. These were a minority, often on life-long anticoagulation. Warfarin was routinely discontinued prior to surgery, and 5000 units of dalteparin were injected during the days warfarin had been discontinued. Patients with recanalization procedure and stenting were given dalteparin 5000 units daily for seven days and nowadays we consider full anticoagulation on these patients after successful intervention.

CONCLUSION

Venous balloon angioplasty and stenting appears to be a safe, relatively simple, and efficient method to treat iliocaval vein obstruction. An immediate or late failure of the procedure does not preclude later open surgery to correct the obstruction. Associated reflux may be controlled subsequently when necessary. Open bypass surgery will probably be reserved for those patients in whom stenting initially could not be performed for technical reasons, late failures that cannot be adequately disobliterated, and long total occlusions, which appear to have a poorer result.

The patients with chronic venous disease are younger, will live longer, and have a better prognosis as compared to patients with arterial atherosclerotic disease. Therefore, venous stenting must maintain the clinical improvement and high stent patency over a longer period of time. Longer-term results are now appearing and the initial favorable result appears to be maintained. The long-term effects of stents in the venous system are still not fully known. Several more years of monitoring is required to assess the efficacy and safety of this therapeutic modality in venous disease. In addition, further research on understanding the nature of venous obstruction and development of reliable methods to test hemodynamic consequences are needed.

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C H A P T E R

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Endovenous Management of Iliocaval Occlusion

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INTRODUCTION

Endovenous reconstruction of chronic iliocaval obstruction is one of the more challenging of all major endovascular procedures. The underlying pathology is complex, as it is frequently the result of multiple episodes of deep vein thrombosis (DVT). In the mid 1980s, venous stents were successfully used to treat obstruction associated with malignancy and Budd-Chiari syndrome.[1–3] Although the majority of procedures are performed fluoroscopically, Zhang reported success with ultrasound-guided caval stent placement in 83 patients with Budd-Chiari related IVC obstruction.[4] The percutaneous approach offers an alternative to surgical bypass or prosthetic replacement of the inferior vena cava (IVC). In addition to being more invasive, deep-vein surgery often includes an arteriovenous fistula to maintain patency of the new conduit. The surgical approach provided durable clinical results in selected cases.[5–8] Caval thrombectomy is a relatively less invasive technique for removal of acute venous obstruction, but not organized thrombus.[9,10] As experience with thrombolytic agents and metallic stents evolved, the indications for percutaneous caval procedures expanded to include treatment of thromboses associated with nonmalignant conditions such as liver transplantation, Klippel-Trenaunay, and hypercoagulability.[11–13] The majority of patients have been treated for acute thrombotic complications. Percutaneous treatment of chronic IVC and iliocaval obstruction has been reported in relatively few individuals.[13–16]

The IVC syndrome is secondary to central vein obstruction and inadequate collateral flow and/or recanalization of occluded segments. This leaves the patient with a critical mass of poorly compensated obstructing thrombus that causes venous hypertension. The endovascular alleviation of the obstruction requires interventional skills with percutaneous techniques, familiarity with thrombolytic infusions, and experienced judgment in selection and placement of metallic stents. Moreover, the interventionalist may need an entire team to manage the demands of serial visits to the angio suite, complicated infusion systems with high maintenance monitoring schedules on the ward. Some reconstructions are less complex. The wire may traverse the obstruction without need of thrombolysis, making it possible to position stents during the initial encounter. Other patients may require patience for thrombolytic infusions and sequential repositioning of catheters and wires.

The length of the obstruction can include bilateral iliofemoral segments in addition to the infrarenal cava. Manipulation of wires and balloons in the long-occluded cava bears the burden of preventing any misstep that could precipitate a retroperitoneal bleed in a fully anticoagulated and lytic patient. Therefore, the iliocaval procedure is likened to the climbing of a mountain, replete with false summits, where the interventionalist must take every step with great care and purpose, knowing that the tedious sequence of maneuvers will enable the safe passage of guidewires from below the inguinal ligament to above the renal veins. Ultimate success requires determination to solve each patient's vascular puzzle, by constructing a new endovenous pathway to reconnect inflow with a patent venous segment beyond the obstruction.

EVOLUTION OF ENDOVENOUS THERAPY

The primary tools of endovenous surgery can be separated into sheaths, catheters and wires, balloons and stents, and thrombolytic therapy. The imaging equipment includes

duplex ultrasound, handheld ultrasound, computed tomography, magnetic resonance imaging, and digital fluoroscopy. The selection of wires and catheters might vary with the physician, and we state our preferences in the technique section. However, the history and concept of balloon angioplasty, stents, and thrombolysis form the basic armamentarium of the interventionalist treating acute and chronic iliocaval obstruction with a minimally invasive approach.

ANGIOPLASTY

As a general principal, balloon angioplasty, alone, is not very effective in treating venous stenosis. Rather than effecting remodeling of a purposefully injured arterial wall, in occluded veins, there is some "give" as intimal hyperplasia is compressed, but the recoil is significant. Therefore, although the balloon can be inflated, there is little permanent effect from expanding the site. However, prior to stents, balloon dilatation became an option in the treatment of Budd-Chiari syndrome caused by membranous obstruction of the IVC and/or hepatic veins.[17] Use of the double-balloon technique on the membrane showed a high degree of technical success and resulted in regression of symptoms. Good initial results were reported in patients with segmental, nonmembranous obstruction of the IVC as well. But, as in Budd-Chiari syndrome, relief of venous narrowing was only temporary and the restenosis required repeated dilation. Balloon angioplasty became an adjunct to stent deployment in the early 1990s. In anticipation of stent placement, dilatation may be necessary to permit passage of the stent delivery system through the lesion. When the 5 F end-hole catheter will not advance, it may be helpful to dilate the tract with a 3 to 4 mm balloon. Following stent deployment, the balloon fully expands the self-expanding metallic prosthesis and apposes the struts against the irregular vein wall.

METALLIC STENTS

The pioneers of venous stenting were Cesar Gianturco and his colleagues in Houston who designed and tested stents in the venous system as early as 1969.[18] It was almost 15 years later when initial reports of caval stenting for treatment of malignant obstructions appeared in the literature.[19,20] The stainless steel Gianturco Z stent™ (Cook, Bloomington, IN) was used to treat Budd-Chiari–related hepatic and IVC obstruction with good technical success rates but with a notable incidence of intimal hyperplasia and stent migration.[21] Axial force was decreased and hook modifications were made to address these issues. The self-expanding woven stents do not have hooks. Whereas overlapped diamond cut Nitinol stents will lock struts, the smooth Wallstents™ will slip on each other. If there is not good apposition to the wall, or the cava expands with valsalva, migration can occur. For this reason, it is important not to place stents in normal vein segments that might expand. The displacement of a stent to the right atrium or pulmonary artery can be life threatening.[22] Pericardial tamponade can occur from atrial perforation. It is necessary to emergently snare the displaced stent via a jugular access and address the pericardial effusion appropriately.

Stents now have been placed in the lower extremity venous system for 20 years. However, there is very little longitudinal follow-up of stent patency. Stainless steel Gianturco stents were initially used to treat malignant conditions and the patients were palliated in their short survivals. However, now we are placing stents in chronically damaged veins of young individuals who expect a normal life span. Standards for managing and monitoring patients are not established. In our practice, we follow patients with annual duplex exams to document patency. The long-term assisted patency for iliac stents reported by Neglén and Raju was 92%.[23] Restenosis occurred more often in patients with thrombotic disease, and in those with thrombophilia, whose stents extended into the femoral vein. Restenosis is suspected when edema or venous claudication recur. It can be seen with intravascular ultrasound and is effectively treated with balloon dilatation.[23]

The advantage of the Z-stent remains the availability of large diameter stents for treating wide vessels such as the superior and inferior vena cavae. However, for treatment of venous stenosis and occlusion in medium size vessels, such as the iliofemoral segments as well as the chronically occluded IVC, the smaller profile, self-expanding metallic stents are preferred. They have longitudinal flexibility and a lower profile suitable for percutaneous entry at the popliteal site. We find the Wallstent™ (Boston Scientific, Natick, MA) serves as an excellent conduit and maintains a high degree of patency in the IVC and large veins of the pelvis and thigh. The commonly used diameters are 12–14 mm, but the stent also is made in 16 and 18 mm widths. The larger stents require an 11 F sheath and are more difficult to deploy. We prefer stents that pass through a 7–9 F size sheath that includes 10–14 mm. Stent size and length are estimated with the help of balloons. If a fully inflated 12 mm balloon is tight in the vein, then a 12 mm diameter stent will extend to the wall when deployed. Dilate the balloon and try to move it up and down. If it slips easily, the stent diameter should be larger than the balloon. IVC stents are deployed in a parallel cross-over configuration that provides an individualized outflow system for each limb (see Figure 61.6). Stents are placed in tandem, with larger stents more proximal. Overlap

should be at least 1–2 cm to prevent separation with foreshortening. A number of self expanding Nitinol stents are available in 8–14 mm diameter with length ranging from 4–10 cm. Although they do not have the issue of foreshortening like the Wallstent™, they remain more difficult to see under fluoroscopy. This may be a disadvantage in the iliocaval region. Balloon expandable stents are not advocated for the venous system, since longitudinal flexibility is desirable when stenting long vessel segments. The majority of venous stents placed in the lower extremities have been positioned in the iliac segments. Approximately 10% of iliofemoral thromboses extend into the IVC.[24] If the distal IVC is occluded, extension of the stents above the occlusion is necessary.

THROMBOLYTIC THERAPY

The immediate objectives of acute thrombus removal include prevention of pulmonary embolus, restoration of venous flow, and preservation of venous valves in the affected extremity. Minimally invasive technique utilizes percutaneous access with coaxial delivery systems for interventions. Ideally, the lowest effective concentration of lytic agent, delivered at a rate and volume designed for the amount of thrombus involved, will be infused through a multislit or side-hole catheter embedded in the occlusion. The goal is to use the least amount of drug that provides the best result in the shortest time without bleeding complications. Best result may mean total lysis in acute thrombosis and guidewire passage in the chronic case. The discovery of chronic stenosis associated with acute thrombosis is common. When streptokinase was introduced in the 1970s, the hope was that enzymatic dissolution of thrombus would be effective, safe, and less traumatic than surgery. Although effective, the early use of peripheral vascular thrombolysis was associated with bleeding complications, in part due to application of the agent via open access to the vessel. Since that time, we have seen an evolution of both thrombectomy and thrombolytic therapy for use in acute deep vein thrombosis.

The main principle in thrombolytic therapy is effective and efficient delivery of an agent to the thrombosed vascular segment(s). As early as 1957, Fontaine and Mahorner et al. used anticoagulants postoperatively to prevent the rethrombosis after thrombectomy. In 1983, Greenwood et al. reported on a patient with Budd-Chiari syndrome following viral myocarditis. Urokinase (UK) was given through an IVC catheter as a local infusion in large doses. The loading dose was 308,000 IU (4,400 IU/kg), followed by 4,400 IU/hr as continuous infusion. After 55 hours of infusion, there was marked improvement in the flow in the IVC. The patient's pain, ascites, and edema rapidly resolved.

Thrombolytic treatment of acute deep vein thrombosis was reported by European colleagues in the 1970s and 1980s.[25,26] It was clear that the complications related to systemic streptokinase and heparin partially annulled demonstration of the benefits of thrombolysis. Their immediate results showed improved thrombus resolution with thrombolysis compared to heparin. Unfortunately, fear of bleeding complications prevented widespread adoption of thrombolysis. In the United States, important technical modifications were made to reduce the incidence of major bleeding. Urokinase became the preferred lytic agent and catheter-directed methods were borrowed from the successful arterial application.[27,28]

Between 1980 and 1999, peripheral vascular thrombolysis was largely performed with urokinase (Abbokinase, Abbott Laboratories, Chicago, IL). This agent was preferred over streptokinase for the safety margin relative to bleeding complications.[27] Reconstruction of manufacturing facilities led to the unavailability of urokinase between 1999 and 2001. Alternative lytic agents such as alteplase (Activase, Genentech, Inc. South San Francisco, CA) and reteplase (Retavase, Centocor, Inc. Malvern, PA) were used in peripheral interventions, despite a shared experience of an increase in bleeding complications, compared to urokinase.[29,30] After dose adjustments for concomitant heparin, interventionalists became more familiar with t-PA, and achieved similar immediate and long-term results with lysis. However, the popularity of catheter-directed thrombolysis for DVT faded after urokinase left the market. When UK returned in 2002, physicians no longer felt compelled to readopt the traditionally favored drug since they had collectively discovered the merits of the less expensive synthetic drug t-PA.[31]

Since 1999, second and third generation tissue plasminogen activators, including alteplase and tenecteplase, have become the most commonly used agents. Newer, more direct-acting agents are being developed. Most recently, alfimeprase trials have been reported and it appears to be a fast and safe lytic agent capable of shorter, more effective infusions.[32]

In larger axial veins, effective thrombolysis is best achieved with catheter delivery utilizing multisidehole infusion catheters and wires.[33] Acute thrombus, less than 14 days duration, dissolves rapidly with catheter embedded infusions of urokinase or alteplase. Chronic obstructions respond more slowly, and the thrombus does not resolve. Rather the lytic infusion serves to soften the organized thrombus and make fenestrated thrombus and synechiae more amenable to guidewire and catheter traversal, thus permitting the interventionalist to perform a sequence of dilatation and stent placement. Analysis of National Venous Registry (NVR) data suggested thrombolysis of chronic thrombus was unsuccessful.[24] In truth, images of distal veins often look as

abnormal after lytic infusion as they do before. Whereas comparison images show dramatic difference when lysing acute DVT, the phlebographic appearance of chronic venous obstruction changes less, even though the venous flow can improve significantly. Interpretation of static contrast images fails to explain the clinical improvement in patients after thrombolytic infusion for chronic obstruction. Reducing venous resistance, by augmenting small and medium size venous channels, does not dramatically alter the post-infusion images, but it is an important adjunct to stenting larger veins. Reestablishing continuity of deep/venous flow from the foot to the cava, has proven to give the best hemodynamic and clinical results.

Physicians attempting to recanalize chronic thrombus may fail to advance the wire or stay intraluminal if they do not infuse a thrombolytic agent prior to and during the wire recanalization phase. Only short, subtotal occlusions can be readily treated without lytic therapy. In treating chronic occlusions, we have the impression that a thrombolytic infusion can “soften” more organized thrombus and thereby facilitate passage of wires and catheters. Although catheter-directed thrombolytic therapy has been shown to be most successful in removing acute thrombus, in chronic conditions, clinical improvement observed after thrombolytic infusion is often greater than any image would suggest. That is because improvement of venous flow, particularly in the calf, depends on the cumulative effect of many unnamed veins remaining patent. Restoring flow in these small conduits can make a significant clinical difference. Real-time phlebography with digital or video recording can demonstrate a clear difference in rate of flow by comparing the rate of contrast clearance before and after thrombolytic infusion. Vascular physiology and fluid dynamics studies show how flow in a tubular conduit is proportional to r4, where r represents the radius. If we apply this concept to venous flow, we see that augmenting multiple occluded or tiny lumens from <1 mm to >2–3 mm significantly increases venous flow despite minimal change on radiographic images. According to this principle, Pousseille’s Law, delivery of thrombolytic agents to the extremity via catheter or flow-directed techniques can promote flow by enlarging the residual lumen. Although not restored to original caliber, lysing acute and subacute thrombus, superimposed upon chronic organized thrombus, increases the luminal diameter. This may not produce a dramatic change on x-ray images, but the increase in flow can be documented with duplex and correlated with post-treatment clinical improvement. Ambulatory venous pressure, as indirectly measured with air plethysmography, should decrease as resistance to flow decreases. However, in our exams, the numbers often do not reflect the degree of clinical improvement. Reasons for this are complex and most likely involve the effects of long-standing obstruction on valves and the calf muscle pump.

MECHANICAL THROMBECTOMY

Thrombectomy refers to physical removal of soft, fresh thrombus. The idea of doing this with a small, percutaneously inserted device is that it atraumatically “vacuums” the thrombus out of the vessel. Such a device would offer the speed of surgical intervention with the advantage of minimally invasive therapy. The Fogarty balloon, a standard tool for rapid thrombus debulking, requires a surgical incision.[35] A number of new devices have emerged, and their design benefits and limitations are discussed in several review articles.[36–39] The objective of the newer designs is thrombus removal with a small-profile, over-the-wire device that can be introduced percutaneously. Most devices provide a small pilot lumen that leaves a substantial amount of residual thrombus. The debulking ability varies according to the device as well as the thrombus composition; the devices do not perform well with organized thrombus.[40] The devices are geared to vessels less than 10 mm in diameter. Both over-the-wire and wireless versions are available. They are not steerable. Residual mural thrombus persists in most vessels, particularly larger veins such as the iliac and cava. The endothelium can be injured and result in rethrombosis as well as intimal hyperplasia. The potential for valve damage has been studied in animals but it is hard to determine in humans.[41]

In general, the debulking seems most appropriate in patients who cannot receive thrombolytics. However, many of these patients, such as elderly post-op patients, cannot receive heparin either. Without anticoagulation, rethrombosis occurs rapidly. In our experience, the debulking process rarely decreases the overall time of the procedure, since additional thrombolysis is necessary to remove residual thrombus for optimal results.

Some devices combine mechanical and pharmaceutical properties to accelerate restoration of flow. The Trellis™ (Bacchus, Menlo Park, CA) device is a combination of balloon, infusion catheter, and wire. The thrombolytic agent is delivered between the occluding balloons. The perfused thrombus is then subjected to gentle mechanical disruption by an oscillating sinusoidal wire positioned between the balloons. This allows contained thrombolysis, thus limiting systemic exposure to the lytic agent. The device allows rapid aspiration of lysed thrombus, through the dual lumen design, but anticoagulation is still necessary. The power pulse-spray concept of the Angiojet™ (Possis, Inc., Minneapolis, MN) is also a combination of powerful delivery of a lytic agent with a thrombectomy catheter.[42]

Despite the reported speed of mechanical thrombectomy, we have used all available devices and most of the time we find there is still a need for overnight thrombolysis. The devices are expensive and require set-up time and technologist familiarity with each design. The use of mechanical thrombectomy may shorten the time until flow is restored,

but they may not lessen the overall time to completion, especially if catheter-directed thrombolysis is needed after the debulking process. But the concept is so appealing, we continue to look for the ideal instrument. The main categories of devices are:

- Balloons, available from 5- to 14 Fr sizes, can be used with or without guidewires as a relatively inexpensive thrombectomy tool. Positive features include speed and cost-effectiveness, and negative features include a higher incidence of incomplete thrombectomy and distal embolization.
- Wire baskets, mostly represented by the Arrow PTD (percutaneous thrombectomy device), the Bacchus Solera, Rex Medical Cleaner, and MTI Castaneda Brush, all use a rotating basket or a fixed one with an inner rotational structure to fragment the thrombus at higher speeds.
- The hydrodynamic Microvena ATD (Amplatz Thrombectomy Device) uses a negative pressure created by a recirculating vortex coming from antegrade high-pressure fluid jets along the shaft and retrograde negative pressure at the tip of the catheter.
- Flow-based devices explore the Venturi/Bernoulli effect, which is based on fast-flowing positive pressure fluid jets that are directed to a negative pressure exhaustion lumen of the catheter. The resulting negative gradient pressure aspirates and causes fragmentation of thrombus. This category is represented by the Boston Scientific Oasis, the Possis AngioJet and Expedior, and the Cordis Hydrolyser.

Again, most devices provide only a small pilot lumen that leaves a substantial amount of residual thrombus. They do not perform well within organized thrombus; however, patients with multisegmental acute venous obstruction, with contraindications to lysis and surgery, now have the option of mechanical restoration of venous outflow, minimizing complications and leaving an opportunity for optimal venous reconstruction with adjunctive angioplasty and stent deployment.

CLINICAL ASPECTS OF ILIOCAVAL OBSTRUCTION

The clinical presentation of inferior vena cava occlusion comprises a wide spectrum of signs and symptoms of venous hypertension. The recruitment of collateral pathways may be adequate, as well as occult, and some individuals will remain symptom free. Symptomatic individuals present with edema and a variety of signs and symptoms of venous hypertension. The severity of symptoms implies inadequate collateral inflow in the face of poorly recanalized, multisegmental obstruction. Although not as common as isolated iliofemoral thrombosis, patients with iliocaval involvement represented between 1 and 10% in the reported series.[15]

Acute caval thrombosis commonly presents with bilateral lower limb edema, unexplained recent weight gain, and in some, back pain. The lack of collateral flow causes lower limb edema, discoloration, and discomfort. Patients have no difficulty recognizing the seriousness of this condition, even though it may have been a gradual change. Once the critical mass of thrombus interrupts caval flow, acute venous hypertension progresses rapidly. Alternatively, chronic caval occlusion is sometimes difficult to diagnose. Occult central venous problems can be indicated in duplex waveform analysis, where the loss of phasicity can provide a clue to more proximal obstruction. (See Figure 61.4)

IVC occlusion often results in bilateral lower limb edema, but occasionally, a single limb is most affected and the discovery of caval occlusion is a surprise. Prominent collateral veins may be seen on the lower anterior abdominal wall or in the region of the pubic symphysis (see Figure 61.1). Unilateral or bilateral lower limb varicosities may be present. Advanced skin changes including hyperpigmentation, lipodermatosclerosis, and ulceration are common with IVC syndrome (see Figure 61.2). In two of our patients, venous stasis changes led to below-the-knee amputation years before the caval obstruction was identified. Patients often report that leg elevation does little to alleviate edema. Prolonged sitting can cause a vague inguinal ache often described as a constant sensation of fullness in the groin area, which becomes

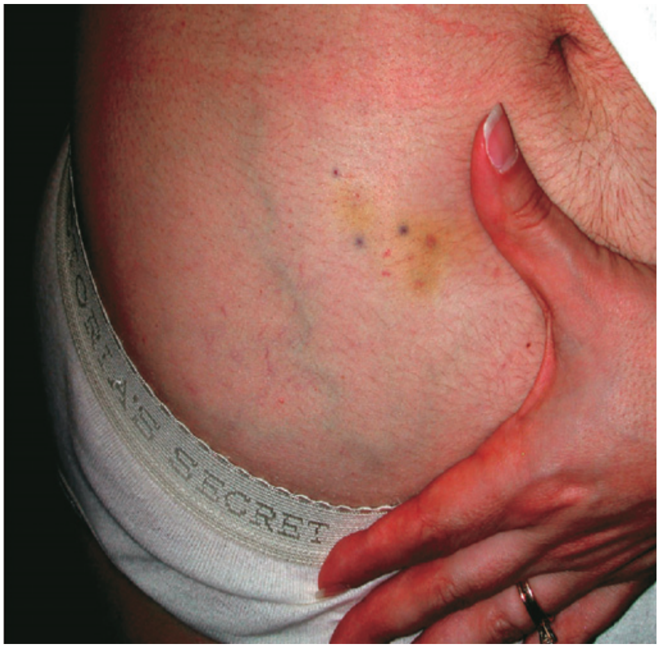


FIGURE 61.1 Prominent lower anterior abdominal wall veins seen on a young woman with iliocaval obstruction for 2 years are a pathopneumonic sign of IVC obstruction. The collateral veins become unapparent after endovenous correction of caval occlusion.

FIGURE 61.2 Twenty-two-year-old male with long-standing iliocaval obstruction, suspected to have occurred shortly after birth. Within two years of his initial episode left femoral-popliteal thrombosis, at age 20, he had a recurrent DVT and developed a stasis ulcer on the medial anterior calf. Evidence of varicosities in his teenage years was an additional sign suspicious for central venous obstruction.

worse with stair climbing. Patients frequently report dyspnea on exertion, even in the absence of any history of pulmonary embolus or respiratory ailments. They may have been told they have asthma. One patient presented with hematuria due to bladder varicosities. In two young patients, presenting at age 17 and 21 years, caval occlusion probably occurred near birth, since each had a single left kidney with compensatory hypertrophy. The common use of central lines in premature and young infants has created a juvenile population with the sequela of central venous thrombosis. The incidence of catheter-related deep vein thrombosis is estimated to be 3.5 per 10,000 hospital admissions, whereas the IVC is affected in approximately 10% of pediatric DVT cases.[43] In a longitudinal study, 40 children, diagnosed with IVC thrombosis between birth and 13 years of age, were followed for up to 20 years after recognition of an early thrombotic event.[44] Among the patients, 21 were identified with extensive IVC thrombosis. During follow-up, complete resolution was seen in four cases; one underwent thrombolysis, two surgeries, and one spontaneous lysis. Obstructive IVC thrombus persisted in the iliocaval segments in 17 children, including six who received thrombolytic therapy. Varicose veins were present in 12/17 (71%) and post-thrombotic syndrome in 7/17 (41%). Analysis suggested that 30% of children with unresolved caval obstruction will develop post-thrombotic syndrome within 10 years of the initial thrombosis. In the young patients we treated, they were asymptomatic until the acute thrombosis of the left iliofemoral segments at ages 21 and 17, respectively. In one patient, this happened after sliding into base playing softball and in the other, after a summer job where he leaned over a large bin husking corn. As in many patients, the investigation of an acute lower limb deep vein thrombosis led to the discovery of previously compensated underlying caval obstruction of indeterminate age.

The majority of patients with long-standing venous insufficiency, secondary to obstruction, are seen by primary care physicians long before they are referred to a vascular specialist. Patients commonly report that they have been told there is not much available for treatment of PTS other than compression. They may have a remote history of iliofemoral DVT and no suspicion of central venous obstruction. Alternatively, they may have a prior diagnosis of iliocaval occlusion, or have been told that the IVC is absent after phlebography or if cross-sectional imaging with CT or MRV have been performed. Large collaterals, seen on computed tomography (CT), have even been interpreted as lymphadenopathy and led to a search for malignancy.

THE ENDOVENOUS PROCEDURE FOR ILIOCAVAL RECONSTRUCTION

Patient Referrals

Acute inferior vena caval thrombosis is almost invariably associated with underlying vascular pathology that went undetected until a set of circumstances resulted in thrombotic obstruction. The combination of hypercoagulability, immobilization, surgery, and remote trauma often play a role in caval thrombosis in younger patients, whereas malignancy may be more common in older patients. Acute IVC thrombosis patients are generally in the hospital, admitted to the medicine service. The vascular specialist is consulted along with the hematologist. Alternatively, the patient with a post-thrombotic syndrome has previously received standard therapy for deep vein thrombosis and has failed to respond. The majority of these patients ultimately are referred to a vascular surgeon for evaluation of disabling venous hypertension and/or stasis ulcer care. Although we have noted a number of patients have a thrombosed caval filter, the filter, per se, cannot be implicated since longitudinal studies have shown a low incidence of caval occlusion with filters.[45]

Initial Evaluation

The procedure for iliocaval reconstruction is, in many ways, similar to preparation for major surgery. The main difference is that the endovenous operation is the series of

interventions that take place in the angio suite over several days, rather than a single procedure occurring, over several hours on one day, in the operating room. The interventional process we have developed over 15 years is best divided into three chronological stages; the workup, the hospitalization and intervention, and the follow-up monitoring. Within the hospitalization phase, there is a sequence of events including the acquisition of baseline contrast studies, the positioning of sheaths and catheters, the initiation of thrombolysis, securing wire access to the portion of the cava above the obstruction, the venous angioplasty needed in preparation for the ultimate positioning of stents to reconstruct the endovenous conduit from patent distal deep veins to the supra-renal IVC. The conversion to oral anticoagulation and mobilization of the patient following removal of the working sheaths proceeds according to protocol. The follow-up phase for a patient with endovenous reconstruction is life-long, but we have found that signs and symptoms of restenosis are most likely to occur within the first 24 months after stent placement.

The clinical severity score as well as a clinical classification is recorded according to published recommendations.[46,47] If a hypercoagulability work-up has not been performed elsewhere, tests for Factor V Leiden and prothrombin gene mutation are acquired. Baseline and calf, thigh, and ankle measurements are obtained as well as anterior and posterior digital photographs. Baseline levels are established for hemoglobin, platelets, white blood cell, creatinine, BUN, protime, prothrombin time, and INR. For patients over 50 years, a baseline EKG is obtained.

A very important aspect of the initial meeting is an explanation of the patient's condition, in language the patient understands, with drawings of the venous pattern (see Figure 61.3). Discussion of the options for reconstructing the venous system involve an explanation of the risks and benefits of thrombolytic therapy, a demonstration of stents, and a discussion about the need for monitoring and anticoagulation after the reconstruction. This mental preparation is not unlike a process that transplant candidates undergo. The intervention implies a major commitment on the part of the surgical team as well as the patient and their family to maintain the desired clinical results long term. This requires carefully monitored INR levels, interval ultrasound evaluation and regular contact with a physician familiar with venous stents. It is important to screen patients for their motivation and ability to work with the medical team. Patients who will not get regular INR tests or who might have limited access to medical care will have a difficult time being monitored adequately. Compliance with anticoagulation and compression are important clinical adjuncts, since, as with many vascular procedures, reconstitution of the deep venous system is palliative. Clinical improvement after restoration of deep vein patency is, in part sustained by compliance with warfarin, for prevention of rethrombosis, and use

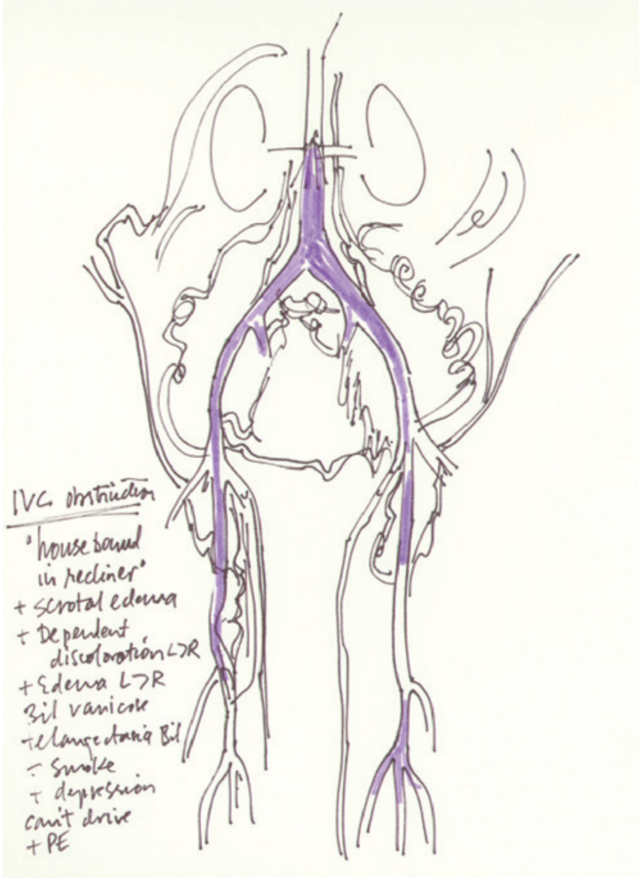


FIGURE 61.3 A drawing of iliocaval obstruction used to discuss the abnormal venous flow pattern and the plan for endovenous reconstruction with the patient and family. Drawings are easier for patients and nurses to understand the procedure. They also facilitate understanding of the radiographic images during the case.

of compression to compensate for the valvular incompetence, which plays a role in venous hypertension associated with DVT.

Diagnostic Workup

Patients referred with symptomatic chronic post-thrombotic syndrome undergo a diagnostic workup. This consists of a one-hour meeting to obtain a history and physical exam and to discuss the findings of any available imaging studies. We have modified for venous obstruction patients to include attention to the difference of segmental flow velocities, as well as the wave forms. This information can provide clues to proximal venous obstruction (see Figure 61.4). Common iliac occlusion and distal IVC obstruction are suggested by loss of phasicity and relatively low velocity at the femoral level. However, flow velocity may be deceptive if there are large collaterals or a prominent internal iliac system, but the waveform will still show little or no phasicity. An ascending phlebogram is obtained preoperatively or

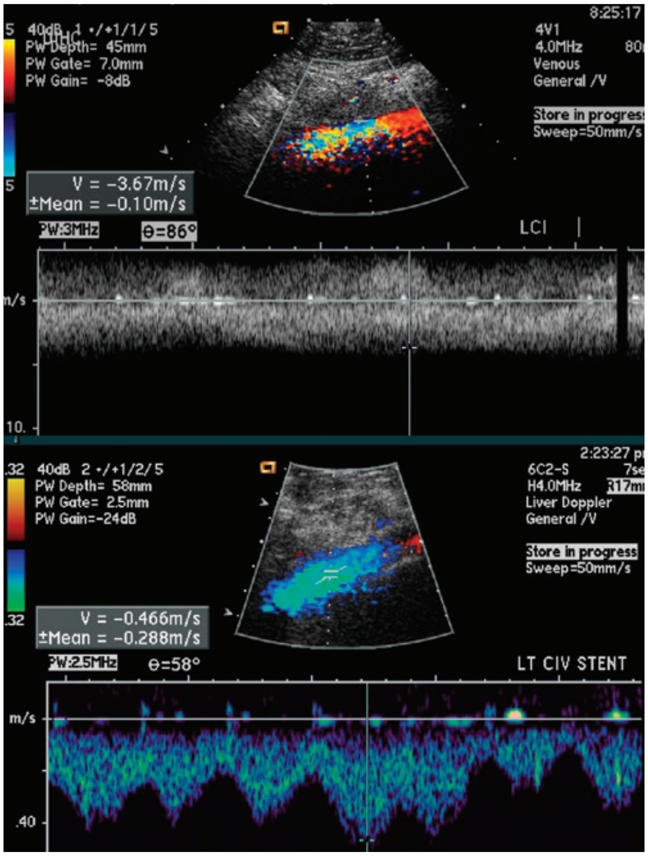


FIGURE 61.4 Duplex images comparing the waveform obtained in the common iliac vein (CIV) segment before and after stent placement. The upper image shows a relatively flat wave, with loss of phasicity, which indicates proximal obstruction. This pattern is also seen in large collaterals near a high-grade CIV stenosis in the May-Thurner syndrome. The inferior tracing shows a phasic waveform with higher velocities. This indicates good return to normal venous flow pattern after stent placement.

as a part of the first-day interventional procedure. It is acquired by manual injection of low-osmolar, nonionic contrast through a 22 g Jelco™ pedal IV placed in a dorsal pedal vein; it is secured with extension tubing combined with a distal-end three-way stopcock. Using 60 cc syringes, contrast is injected into the vein, closely observing for extravasation. This can be difficult, due to high venous pressures, and slow clearance of contrast characterizes the initial exam. It becomes easier as the venous resistance decreases. More detailed pelvic images are obtained once catheter access is obtained via the popliteal sheath.

Three dimensional CT reconstructions and MRV can provide information about pelvic vein and iliac compression. Magnetic resonance venography (MRV) has been compared with contrast venography and ultrasound in detection of DVT. All thrombi detected by contrast phlebograms were also detected with duplex and MRV. There was 98% correspondence in diagnosis of DVT with these modalities.[48] Insurance certification should be reviewed as an initial issue. The therapy is expensive and insurance coverage needs to be authorized with clear revelation of potential codes and costs.

The Endovenous Technique

After review of the imaging studies and evaluation, a patient is scheduled for admission and intervention. A patient with chronic ilio-caval occlusion, which involves both extremities, requires the "full-court press" bilateral popliteal approach. This begins with bilateral placement of pedal intravenous access when feasible. We often use contrast injection to check popliteal anatomy and puncture level. With the patient in a prone position, the popliteal area is prepped and draped. Sterile technique is used with the hand-held ultrasound transducer used to identify the popliteal vein or lesser saphenous. The transducer guide will accommodate the 21 g needle from the micropuncture kit that also includes a coaxial 3/5 F short dilator and an 80 cm .018″ wire. We prefer an 80 cm Nitinol for initial access through the needle. A one-wall puncture is essential. If an inadvertent arterial puncture occurs, leave a small caliber dilator in place if thrombolysis is intended. A 5–6 F 15 cm sheath is then positioned. The sheath is secured with tape or suture. Keep in mind that any puncture can cause incessant oozing when using thrombolysis. Navigation of the occluded femoral, iliac, and caval segments is performed with 4–5 F straight and angled hydrophilic catheters combined with the angled Glide wire (Boston Scientific) or Head Hunter wire (Cook). These hydrophilic tips are lumen seeking. The catheter is advanced as permitted. Stronger 035″ exchange wires may secure the tract for catheter positioning, but these are dangerous wires for probing. Advancing an Amplatz wire into organized thrombus may result in perforation. Whereas this can be tolerated when chronic fibrosis is present, it is best avoided. Smaller .018″ wires are useful for tracking a 2–4 mm balloon that can help augment the pilot lumen when a 5 F catheter will not track over the hydrophilic wire. Keeping in mind that balloon dilatation can also obliterate a tract, never lose access during the guidewire exchange process. A common sequence is initial attempt with 4–5 F combination, where the wire goes far beyond where the catheter will advance. A .018″ wire can allow dilation with a 2–3 mm × 4 cm small vessel balloon. The 5 F catheter can then be advanced a bit more cephalad. With this sometimes tedious sequence of dilate-and-advance, one can ultimately move a wire from below the obstruction to the patent segment above the lesion. Great care must be taken in the area of the caval bifurcation. Many collaterals track parallel to the cava in anterior or posterior planes (see Figure 61.5). Angulation of the image intensifier is necessary to avoid being faked out. Perforations in this region carry the risk of retroperitoneal bleeding, so serial computed tomography may be indicated to monitor for any abnormal accumulation

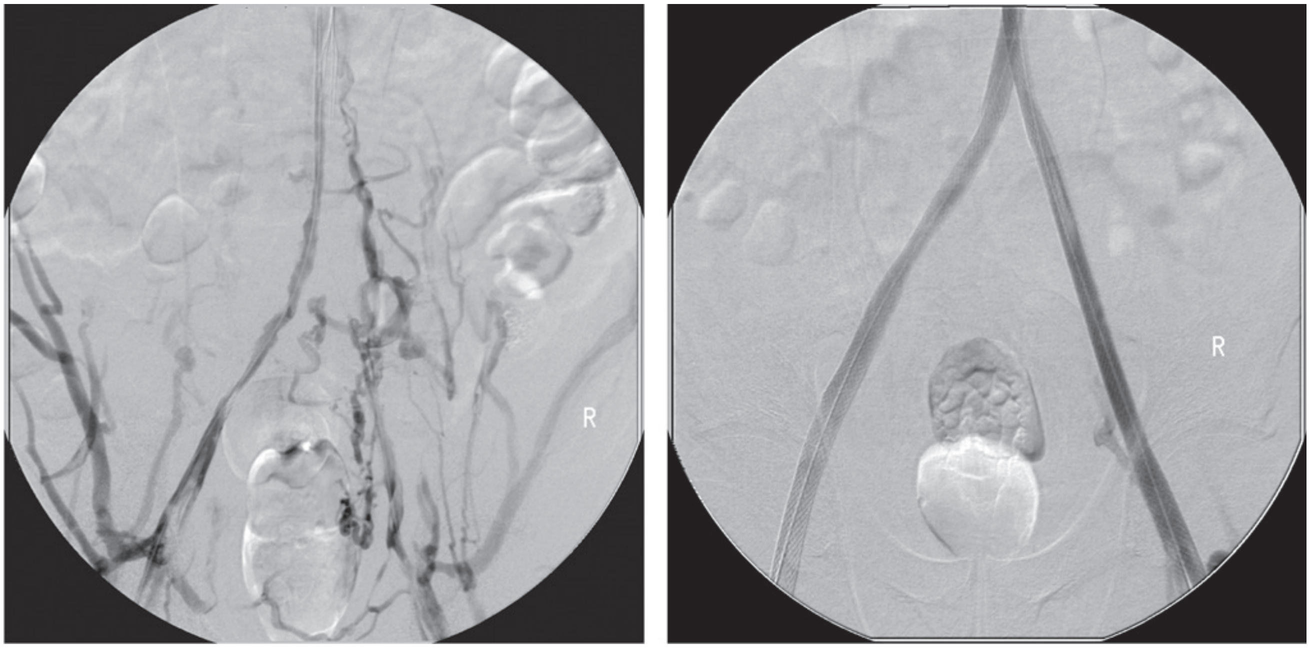


FIGURE 61.5 Digital images show pelvic veins before and after reconstruction of totally occluded IVC and bilateral iliac segments in a 38-years-old patient. Note the prominent circumflex iliac vein as well as internal iliac tributaries that serve as alternate pathways for external and common iliac obstruction. The true lumen, leading from the common femoral level, frequently is seen as a tiny wisp of contrast medial to the iliac circumflex. The second image shows completion phlebogram after placement of bilateral Wallstents™.

of fluid or contrast. Anticoagulation is maintained during all catheter manipulations. We often "park" a catheter at the highest position achieved without force. Forcing a catheter or wire has a high probability of causing perforation. We find that overnight infusion of a dilute lytic agent (10 mg alteplase/liter normal saline) at 50–75 cc/hr can change the venous terrain enough to facilitate progress toward the goal of safely passing an intraluminal wire through the total occlusion.

Once the 100 cm 5 F straight or angled end-hole catheter can be positioned in the open cava, usually above the renal veins, an exchange length 035″ Amplatz wire is positioned. In the event that the hydrophilic wire will not traverse the lesion from below, it may be useful to advance a wire/catheter from above. This will require an internal jugular approach. It is hard to do, in the middle of the case, since the patient is prone. The popliteal sites have to be secured and the patient turned supine. Working from below is a challenge. If the wire passes from above, it may enter a catheter and exit the popliteal sheath. If the wire passes from below, a 5 to 10 mm gooseneck snare can be used to snare the wire tip in the cava and pull the wire through the jugular sheath. This much traction may be necessary to balloon tight caval and iliac lesions without having the balloon slip out of position. After the working wire has been placed from each direction, serial balloon dilatation can proceed. Start with smaller 8 mm × 40 mm balloons. A single 8 × 14 mm balloon can dilate the IVC area. It may be difficult to advance a larger, high-profile balloon through the pilot lumen.

Following sequential dilatation of the cava and bilateral iliac and femoral segments, it is time to select stents. A principle guides stent placement. One must reestablish deep venous flow from a point of good flow below the obstruction to a point of good out-flow, above the obstruction. In an optimal situation, the femoral veins are normal and the lesions involve the iliac segments and the infrarenal cava. We start the stent deployment in the infrarenal cava. Placement of stents in the intrahepatic cava requires great precision and avoidance of extension into the right atrium. We only stent this area if it is clearly diseased and narrowed. This can be deceiving, since decreased inflow causes collapse of the cava and it may appear stenotic when it is merely underfilled. A good way to test this is to inflate large balloons, to see if they are mobile when inflated. If they are easily moved within the lumen, the cava is not that narrow.

Stents are deployed from proximal to distal. An exception would be a very tall patient in whom the delivery system would not reach that level from the popliteal entry. We use the Wallstent or self-expanding Nitinol stent. We have had success with the high extension of cross-over parallel systems coming from left and right (Figures 61.6 and 61.9).

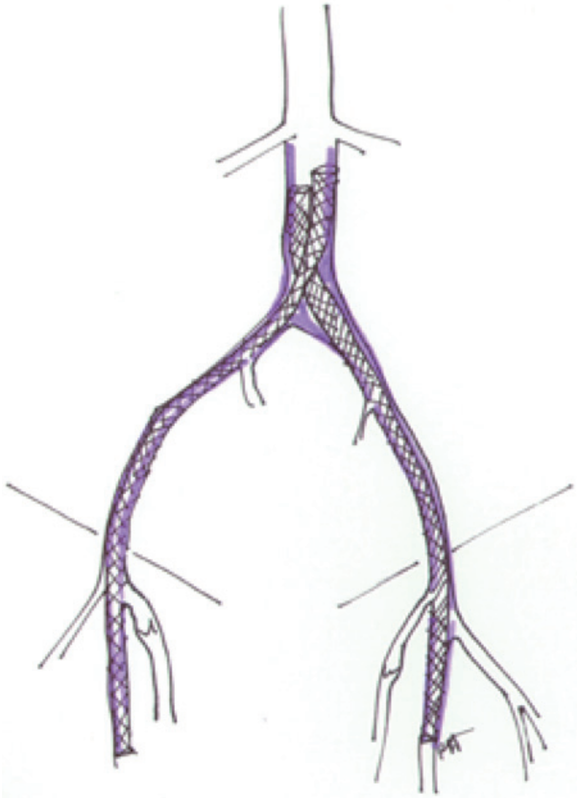


FIGURE 61.6 Drawing shows two parallel stent systems that cross to the opposite side at the bifurcation. This dual column, cross-over configuration is our preferred stent pattern for iliocavel reconstruction.

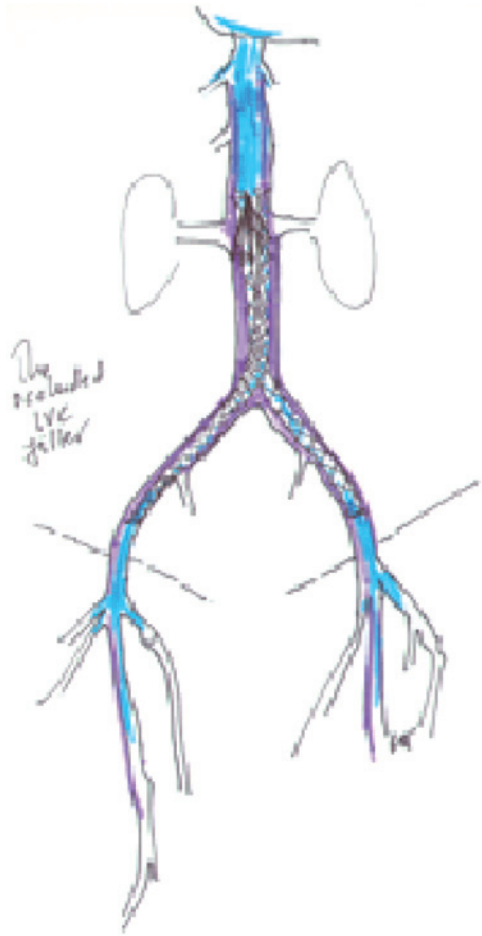


FIGURE 61.7 Drawing depicts cross-over stent system passing through a totally occluded Greenfield filter. Note the upper margin of the stent column is at the level of the filter cone.

An alternative is the "Y" configuration (see Figure 61.10a). The large diameter stent is extended to the bifurcation and the iliac stent is positioned at an angle, but may not extend into the caval stent. A modification of this pattern would be extension of unilateral or bilateral iliac stents into the single distal caval stent (see Figure 61.10b). Often, the symmetry is not maintained after the balloons are removed. One side can be partially collapsed by the force of the other stent. It is for this reason that we evolved the high-extension, cross-over system. In the average-size patient, a parallel series of three overlapped Wallstents™, 12 mm × 90 mm, 12 mm × 60 mm, 12 mm × 90 mm, extend from the renal vein level to the upper thigh. The sequence is intended to have the distal margin of the second stent placed above the inguinal ligament. The extension of the third stent results in a gentle curve of connected stents from the cava to just below the common femoral level. If necessary for flow without stasis, we recommend dilatation and stenting of the femoral vein to a point of spontaneous flow. Spontaneous flow is indicated by contrast clearance from unforced in-flow of unopacified blood. If contrast "sits" in the vein, there is either poor in-flow or out-flow. If the out-flow is stented open, then in-flow may be blocked by the sheath or residual thrombus or both. Pull-back pressure measurements and IVUS can help determine the significance of nonocclusive irregularities. More than 3-mm Hg pressure differential may be important, but there are no good data to confirm this observation. Keep in mind the adage, good flow through a "funny looking" vein is better than bad flow through a perfect stent. The endpoint of stenting is restoration of deep system flow. It is achieved when there is no visualization of collaterals or stasis of contrast with completion venograms. The very large pelvic collaterals may fill slightly, but the main flow pattern is returned to the newly opened stent conduit. Another parameter is duplex velocity; the measurement at the common femoral level returns to 20–40 cm/sec.

Stenting though an occluded caval filter is a special challenge. Careful positioning of the guidewire, through the struts, can be followed by serial balloon dilatation. Note that the wire does not go around the filter but through the struts. There is usually chronic, undissolved thrombus within the filter. It is "stuck" there, but care is taken to do as little manipulation as possible. Self-expanding stents are deployed

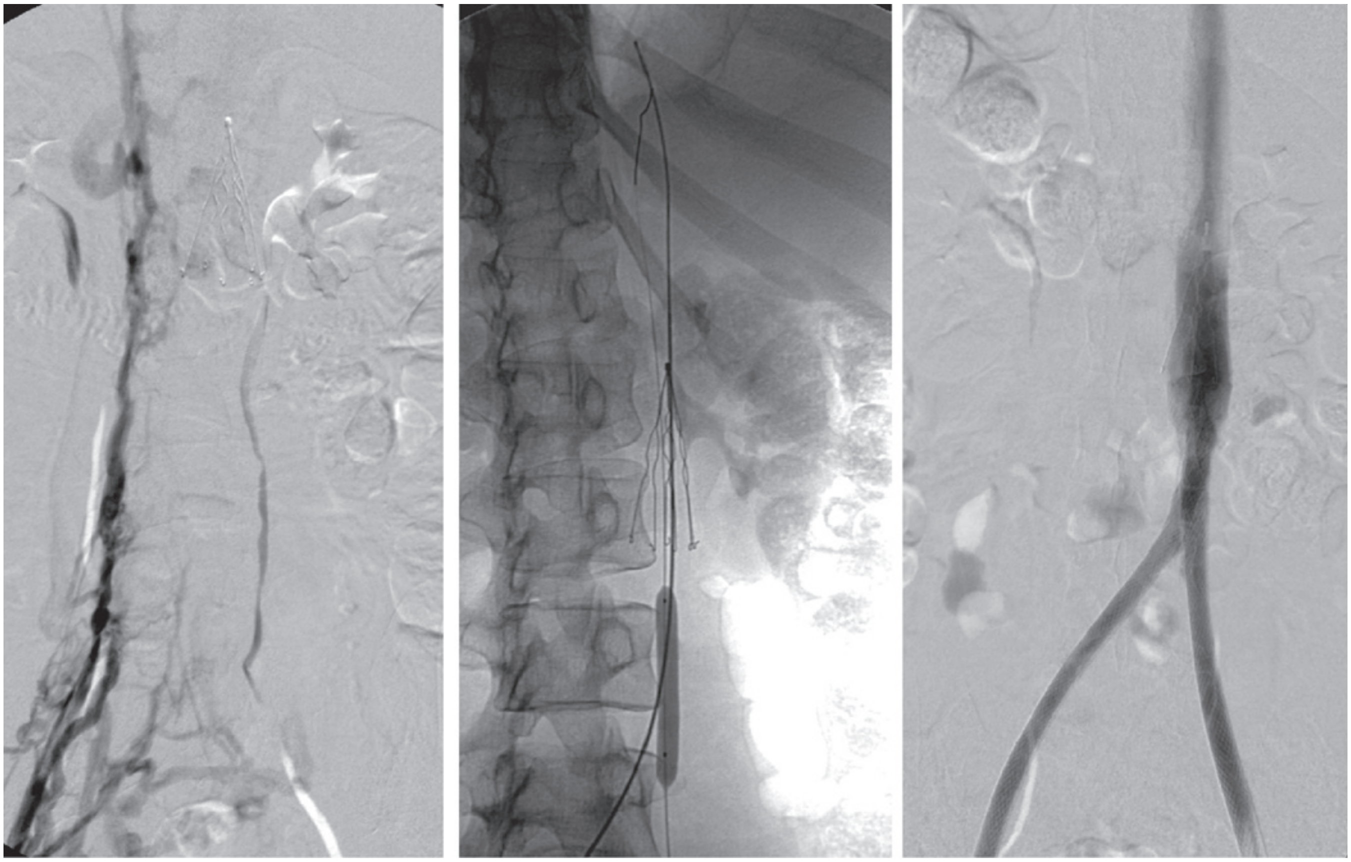


FIGURE 61.8 This 38-year-old female patient had a two year history of ilio-caval obstruction with an occluded Greenfield filter. The first image shows peri-caval collateral with no flow in the IVC. In the middle image, guidewires can be seen traversing the filter. An 8 mm × 4 cm balloon is seen inflated in the distal cava. In order to stent the chronically thrombosed cava, the double crossover tandem Wallstents™ were extended though the filter.

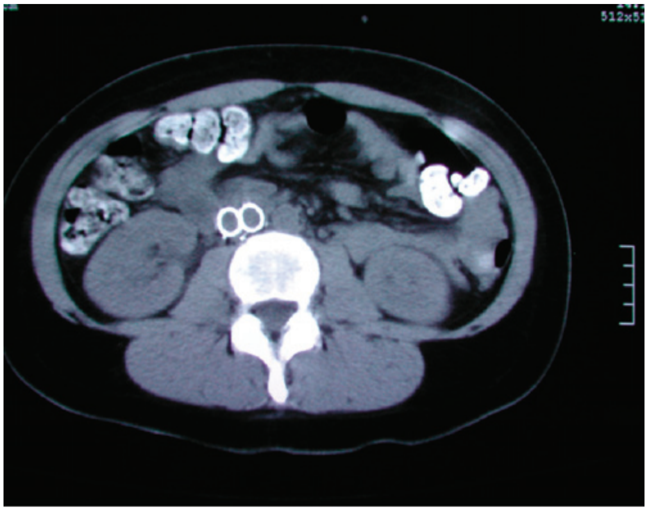
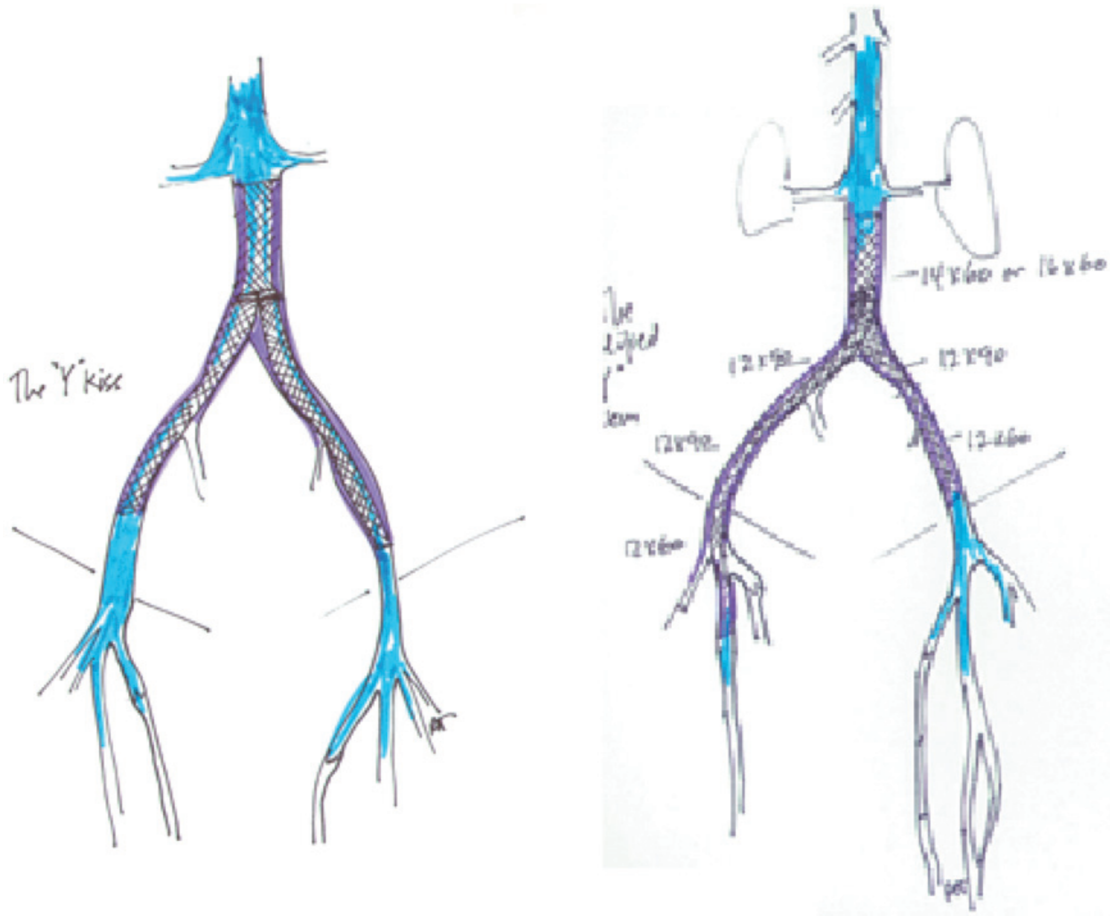


FIGURE 61.9 Cross-sectional abdominal CT of image of patient in Figure 61.8. See the 2 stent lumens, side by side.

simultaneously, assuring that the superior margin is at least 1 cm above the filter strut (see Figure 61.11).

We keep the patient therapeutically anticoagulated with unfractionated heparin. Low molecular weight heparin (LMWH) has not been tested in this scenario and there are anecdotal cases of abrupt rethrombosis when this was attempted. Warfarin and clopidogrel (Plavix) can be started within 24 hours of stenting. A stable, therapeutic INR (>2.0 < 3.0) is required before heparin is discontinued. Popliteal and jugular sheaths can be pulled with the PTT ~ 50 seconds. We do not discontinue heparin. The patient is prone for popliteal sheath removal. Mild manual pressure is placed on the back-wall puncture site and sheath tract for 10 minutes followed by placement of a Coban™ wrap, pressure dressing. The patient does not ambulate for 24 hours after removal of the sheathes. This minimizes hematoma formation behind the knee. A completion duplex exam is obtained before discharge. The INR is closely monitored for six to eight weeks, in cooperation with the patient's local physician, to assure a recommended range of 2.5 to 3.5 is maintained. Annual exam and duplex documentation of stent patency are part of



A B

FIGURE 61.10 Drawings depict the "Y" configuration of stents (left) and the "modified Y" pattern. When using these options, we prefer a caval stent that does not foreshorten upon deployment.

our protocol. When duplex velocities decrease, or patients have recurrence of edema or discomfort, the stents are dilated via a right internal jugular approach in an outpatient procedure.

Clinical Experience

The first endovenous stent was placed in the IVC in 1986 by Zollikofer and colleagues.[21] Between 1986 and 2000, fewer than 100 IVC stent cases were documented in the literature. This included endovenous treatment of benign (67%) and malignant (33%) IVC obstruction. Most of the patients developed inferior vena cava syndrome secondary to acute thrombosis superimposed upon a focal lesion. Catheter-directed thrombolysis of acute caval thrombosis was reported to be technically and clinically feasible by Angle et al.[49] They restored IVC patency in 7/8 patients, and all reported no edema with mean follow-up of 11 months (range 2–24 months). In 2001, Razavi et al. reported a series of 17 consecutive patients with chronic IVC occlusion treated over a six-year period.[14] The mean duration of symptoms was 32 months. Thrombolysis and/or stents were used with technical success in 15 (88%) patients. After mean follow-up of 19 months, primary patency rate was 80% and the primary assisted rate was 87% (13/15). There were no procedure-related complications, although four patients died during the follow-up period, due to underlying disease.

Between 1996 and 1999, seven patients (6 M/1 F) ranging in age from 16 to 72 years (mean 45.4 years) underwent endovascular therapy at Creighton Medical Center, for symptomatic venous insufficiency involving longstanding IVC occlusion.[15] Mean duration of symptoms was 17 years (range 12–25 years) (see Table 61.1). CEAP classification included C4 (3), C5 (2), and C6 (2). Prior to intervention, the mean clinical score was 10.25 and the average and median disability score was 3. All patients wore compression hosiery and were on warfarin prior to treatment. Three patients had a history of pulmonary embolus (PE) treated with a filter (1), a DeWeese caval plication (1), and caval ligation (1). One patient had a prophylactic filter placed prior to back surgery, and this was occluded. Two patients had previous vascular surgery including right popliteal transpo-

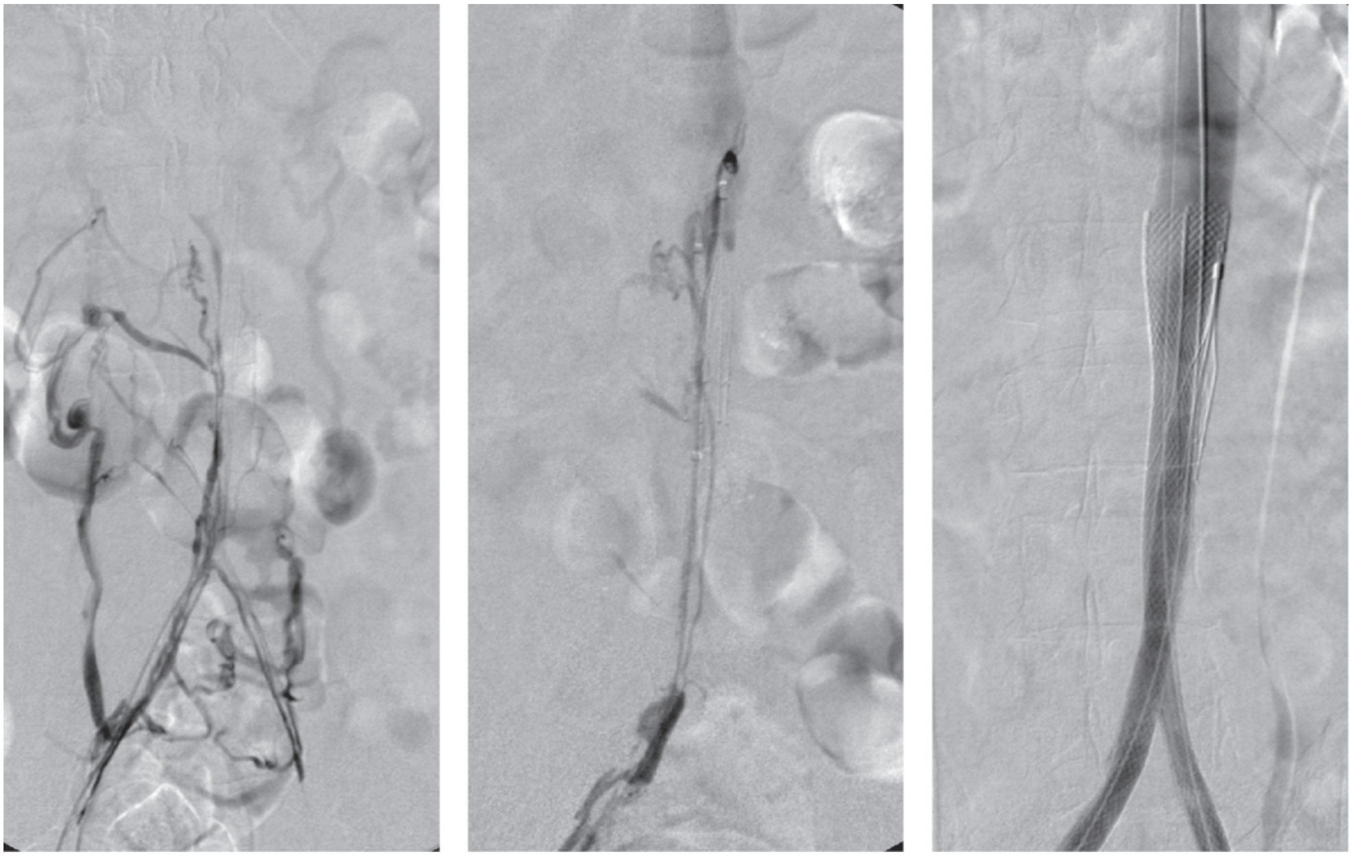


FIGURE 61.11 This series of digital images show totally occluded IVC and iliac veins in a 50-year-old man. The Gunther Tulip™ filter was occluded. The images show the abundance of collaterals that can deceive the interventionalist before the true lumen is revealed. Wire advancement through the obscured lumen can be tedious. Note that one stent system passes though the filter whereas the other column appears to be adjacent to the contracted filter.

TABLE 61.1 Basic Data of First Seven Patients Treated at Creighton for IVC occlusion
1995–1999 IVC Syndrome

		age	1st DVT	duration	
1	m	38	1977	20 y	Fac V
2	m	72	1984	12 y	
3	f	62	1977	20 y	
4	m	38	1981	17 y	AT III
5	m	16	1982	17 y	Pro S
6	m	40	1992	8 y	
7	m	52	1974	25 y	Pro S
mean		45.4		17 y	

sition valvuloplasty (1), and Palma-bypass, left to right (1). Although a question of congenital abnormality was raised in three patients, the etiology of caval occlusion was thought to be post-thrombotic in all patients. All patients had bilateral iliac obstruction. Chronic femoral obstruction was encountered in 10/12 (83%) limbs. Patient 5 presented with acute left DVT extending from the calf to the iliac. Chronic changes were noted in the calf and popliteal regions in patients 5/7 (71%). Reflux was documented in 11/12 (92%) treated limbs, and in patient 6, both superficial and deep valves are incompetent. Two patients had prior below-the-knee amputation due to stasis ulcers and presented with nonhealing ulcers on the surviving limb.

Endovascular reconstruction of the occluded iliac (14) and IVC (7) segments was accomplished in all patients. The median length of stay was eight days (range 6–15 days). Urokinase was used in six patients and a combination of urokinase and rt-PA was used in patient 7. The average dose was 8.8 million IU infused over 48 to 96 hours (range 36–120 hours). The average number of stents placed was 2.8 (range 2–4). In three patients, stents extended the entire length of the IVC. Clinical improvement was noted rapidly in all patients. Long-standing thigh edema decreased over the first five days. Patients often are refitted for a different size of compression stocking. The clinical score decreased significantly after therapy ($p < 0.001$). Disability decreased in six of those treated by one level and by two levels in the youngest patient. In two patients, ulcer healing occurred in <30 days, but reoccurred at 18 months in one, due to poor compliance with warfarin and a recurrent popliteal DVT.

Complications related to thrombolysis included site infection (1), UTI (1), transient hematuria (1), and retroperitoneal hematoma (1). The hematoma occurred in the patient receiving rt-PA and was associated with wire perforation, during stenting, at the site of caval ligation. However, this patient lost more blood at the groin site, where scar tissue from previous trauma and surgery caused oozing at the sheath site.

It has been 10 years since the first patient in this series was treated. Patient 2 survived four years after intervention, and death was unrelated to VTE. His IVC stents were patent by ultrasound at 44 months. Patient 3 underwent a left BKA in 2003 secondary to ischemic arterial disease and complications of diabetes. The stasis ulcer remained healed during the six years following intervention for restenosis of the distal iliocaval stents in 1997. Restenosis was identified and treated in 4/7 (57%). Among the five surviving patients, patients 4 and 5 have not required any reintervention. Their IVC/iliac stents remain patent by ultrasound at 95 and 82 months follow-up. Patient 5 was 16 years old when treated. At age 23, he remains asymptomatic and is therapeutically anticoagulated, due to Protein S deficiency. Patients 6 and 7 each had reintervention six months after stent placement. In Patient 6, the caval stents showed intimal hyperplasia at the proximal and distal aspects. Caval stents were dilated and symptoms of discomfort and associated edema resolved. A second reintervention was performed in 2002 to redilate left iliofemoral stents. The intimal hyperplasia was documented with intravascular ultrasound (IVUS). The left leg symptoms resolved. Patient 7 also experienced an increase in left leg edema at six months. A stenosis at the distal aspect of the common femoral stent was dilated. No further interventions have been indicated during the 74-month follow-up. Patient 1 has been observed for 10 years. He had suffered extreme pain from a stasis ulcer in the right medial malleolar area prior to intervention. Not only did the ulcer heal, after the series of interventions, it has remained closed since 1998. Ultrasound exams in 2005 document continued flow in the ilio-caval stents. In summary, by 2005, mean follow-up was seven years, eight months; the primary patency remained 33% with assisted patency 86% (due to one patient with rethrombosis, which was successfully reopened). Actuarial secondary patency was 100% (see Table 61.2). Clinically, two patients remain asymptomatic. Edema and variable discomfort affect the other three patients but each manages to work and remain active with compression stockings. Each patient affirms their continued clinical improvement following endovascular therapy.

Raju and Neglen reported similar experience with percutaneous recanalization of totally occluded iliac veins in 38 limbs and the occlusion extended into the infrarenal IVC in nine cases.[16] Two cava had an occluded filter. The median length of the occluded segment was 22 cm. The median number of 14–16 mm diameter stents used per patient was three. Diffuse distal chronic venous changes were noted in 88% of treated limbs. The chronic, nonocclusive DVT involved femoral, popliteal, and tibial segments in 62% versus a single segment in 9%. However, distal segmental occlusions were noted in 52% of the limbs; the majority of such tandem occlusions were femoral. Distal femoral lesions were not stented. Mean follow-up was 24 months. He reported actuarial primary, assisted, and secondary patency rates of 49%, 62%, and 76%, respectively. Clinical improvement was gauged with the pain scale where a significant decrease from level 4 to level 0 ($p < 0.0001$) was reported. Sixty-six percent of limbs showed resolution of open ulcers or stasis dermatitis at one year. Reflux was documented in 87% of treated limbs and involved both superficial and deep systems in 65% of these individuals. Perhaps the differences in the long-term iliocaval stent patency rates among separate series reflect variable treatment of distal, tandem obstructions as well as selective use of anticoagulation.

TABLE 61.2 Primary, Assisted, and Secondary Patency Rates Are Derived from Notation of Reintervention for Restenosis, over Time. Two Patients Have Required no Further Endovascular Treatment
Restenosis treatments

	6 mo	12 mo	18 mo	24 mo	3 yr	4 yr	5 yr	6 yr	7 yr
1				X	X				
2						D			
3	X								
4									
5									
6		X				X			
7		X							

In 2004, Robbins et al. reported on two cases to demonstrate the value of endovascular correction of chronic long-segment inferior vena cava obstruction.[13] A young woman, with Factor V Leiden, and a three-year history of progressive right limb edema was diagnosed with caval obstruction following MRV. A series of Wallstents™ were overlapped to reconstruct the iliocaval segments without thrombolysis. The bidirectional or through-and-through access was used to facilitate balloon dilatation and stent deployment at the intrahepatic, infrarenal cava, and right iliofemoral levels. Large diameter stents, 18 mm, were used in the cava, 16–14 mm in the iliac, and 12–10 mm in the femoral. Right lower extremity edema resolved remained absent at six months. The patient was managed with warfarin and clopidogrel (Plavix) for six weeks and 81 mg daily aspirin long-term. The second case involved bilateral lower extremity edema and caval occlusion in a 72-year-old man with a three-year history of edema and venous claudication. The occluded IVC was approached through the patent right common femoral access. A sequence of Gianturco Z stents (Cook), dilated to 16 mm, was used to reconstruct the entire

IVC. The most proximal stent was placed in the intra-hepatic cava just below the right atrium. An additional left iliac lesion was treated with a single 14 mm Wallstent™. The extremity edema resolved rapidly, and he was managed with warfarin and aspirin. The patient was only followed for two months due to progression of his primary liver disease.

CONCLUSIONS

These cases demonstrate the technical feasibility of recanalization of the cava without thrombolysis. Thrombolysis is most useful when the guidewire does not easily traverse the occlusion. The option of endovenous reconstruction is a valuable addition to the vascular specialist. Each procedure may be tailored to the patient's condition. Perhaps, in the future, devices will be designed to facilitate recanalization and debulking of organized thrombus. Surely, the techniques will evolve as we share more data, and new tools are introduced. For now, some hard learned lessons can be summarized briefly. In our experience, the long-term patency of caval stents may depend upon adequate restoration of distal flow, when multisegmental occlusions are present. Establishing continuity of flow throughout the deep system appears to be important to long-term patency. However, stenting below the adductor canal level has been unsuccessful in our experience. The use of large-diameter stents (12–16 mm) is favored, but it has been shown that excessive axial force is associated with intimal hyperplasia.[1] Finally, selective use anticoagulation may promote patency. Patients with a known hypercoagulability factor have a clear indication for long-term therapy. In addition, therapeutic warfarin levels (INR 2.0–3.0) help maintain patency in limbs with chronic residual thrombus in the deep venous system, even when larger, proximal veins are widely stented. Perhaps the most important message from reviewing the endovascular treatment of chronic venous occlusion is an appreciation for the need to aggressively treat more patients with acute DVT in hope of preventing the sequela of unresolved thrombosis.

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CHAPTER

62

Popliteal Vein Entrapment

SESHADRI RAJU

Popliteal vein entrapment is a rare clinical entity. *Anatomic* popliteal vein compression, however, can be demonstrated by imaging techniques in as many as 27 to 42% of asymptomatic individuals with a 34% incidence of bilaterality.[1,2] In the frequency of the anatomic lesion and the rarity of the clinical expression, the entity perhaps resembles thoracic outlet syndrome. Compression of the popliteal vein infrequently (±10%) is associated with companion arterial compression even though the very first case reported by Rich and Hughes in 1967 was.[3] Clinical features are often indistinguishable from other forms of chronic venous disease (CVD) and easily applicable diagnostic testing is lacking. Diagnosis currently depends on awareness of the entity and elimination of other causes of chronic venous insufficiency. Invasive monitoring of dynamic popliteal venous pressure with ankle maneuvers in suspected cases may be specific.[2]

INCIDENCE

The estimated incidence is less than 4% of all cases of CVD, probably much less. Sporadic case reports[4–15] and two series[2,16] can be found in the literature.

CLINICAL FEATURES

Contrary to expectations, the disease is not confined to the young; there appears to be no age or sex predilection.[2] Like other forms of CVD, common symptoms and signs are swelling, pain, and stasis skin changes including ulceration. Limb swelling extending above the knee joint probably rules out the condition as the primary pathology. Venous claudication may be present in some but not all. Cutaneous hyperpigmentation may extend more proximally beyond the gaiter area in some patients. Isolated popliteal valve reflux when symptomatic should arouse clinical suspicion of entrapment, as the former by itself is seldom symptomatic. Entrapment may result in popliteal vein thrombosis.[17]

INVESTIGATIONS

Popliteal vein compression on ascending venography is sensitive, but not specific. Popliteal vein compression should be demonstrated on active plantar flexion; passive dorsiflexion may also reproduce the lesion in some (see Figure 62.1). The site of compression is variable (high popliteal 11%, mid popliteal 39%, low popliteal 18%, and diffuse 32%), thus suggesting varied compressive mechanisms.

Like venography, duplex with ankle maneuvers can also demonstrate popliteal vein compression without any inference to causality of symptoms.[1] Associated popliteal artery compression with ankle maneuvers is present in about half of the limbs without clinical features of arterial insufficiency. Demonstration of arterial compression does not signify functionally significant associated venous compression.

Magnetic resonance imaging[18,19] may display abnormal features of the gastrocnemius muscle that is frequently a part of the compressive mechanism, and it can help rule out other causes of compression such as the Baker's cyst.[9,14]

Abnormalities on ambulatory venous pressure measurement (pedal vein) and outflow fraction by occlusive plethysmography may be suggestive, but these tests are neither sensitive nor specific.[2] Similar comments apply to ejection

fraction and residual volume measurements with airplethysmography (APG).

Dynamic popliteal vein pressure measurements (see Figure 62.2A,B) with ankle maneuvers appear to be diagnostic and useful in assessing outcome after entrapment release.[2]

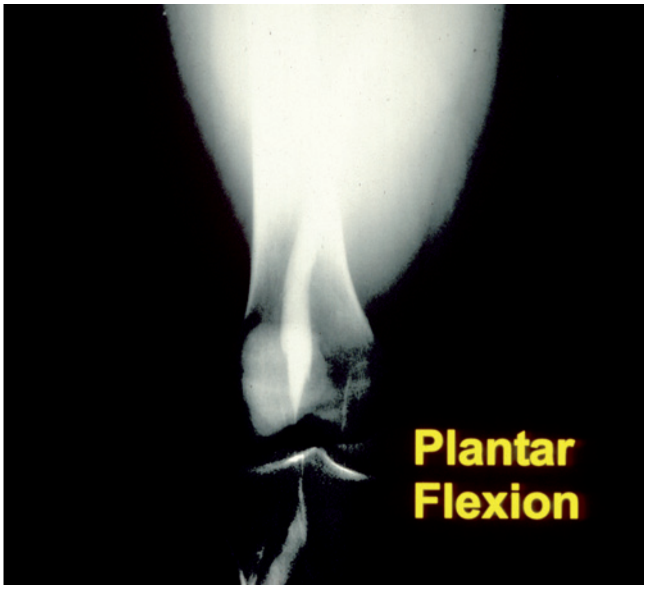


FIGURE 62.1 Popliteal vein compression with ankle maneuvers: mid popliteal (left). Discrete lesions at high and low popliteal locations as well as diffuse lesions (not shown) also occur.

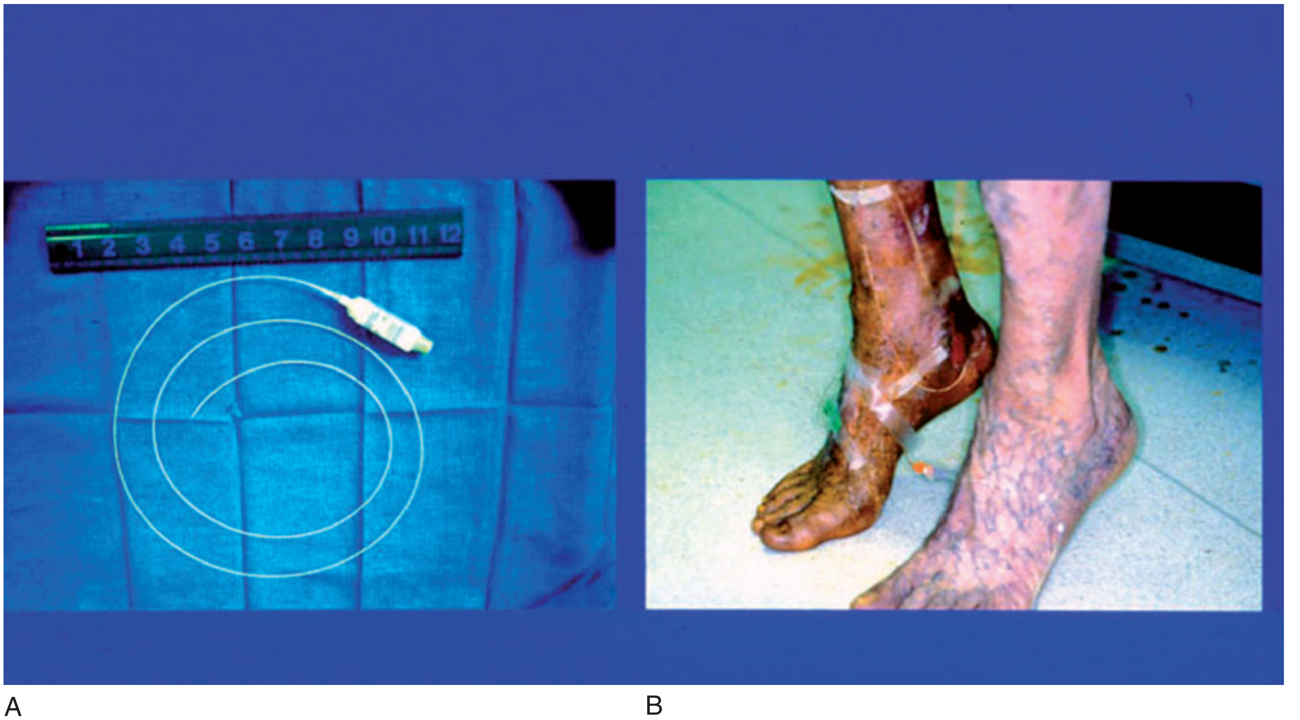
PATHOLOGY

The most frequent compressive mechanism is the gastrocnemius muscle due to abnormalities in the origin of the medial head (see Table 62.1). Postnatal extension of the medial head of the gastrocnemius muscle from the medial femoral condyle to involve portions of the adjacent femoral shaft is a normal event; excessive migration appears to result in compression of the vein. Compression by other muscles

TABLE 62.1 Pathological Features in 30 Cases Undergoing Entrapment Release

Compressive entrapment mechanism	Number
Gastrocnemius Medial Head anomalous origin	18*
Additional 3rd Head of Gastrocnemius	1
Gastrocnemius Lateral Head Origin from Medial Condyle	5
Soleus Sling	3
Thick Perivenous Fascia	13†
Abnormal Course of Vascular Bundle lateral to the Lateral Head	v2
Unknown	v1
Pathological changes in the popliteal vein	**Number**
Sclerosis	13
Pre-stenotic Dilatation	1
Post-stenotic Dilatation	4◆
Post-thrombotic Changes	2

*One case associated with atrophic lateral head.
†Associated with other entrapment mechanisms.
◆Two saccular aneurysms.
By permission: J Vasc Surg 2000;1:631–641.



A B

FIGURE 62.2 **A**. Calf exercise with percutaneously inserted Millar Probes™. The 2Fr catheters have tip-mounted pressure transducers. The catheter tip is positioned in the popliteal vein under fluoroscopy (**B**).

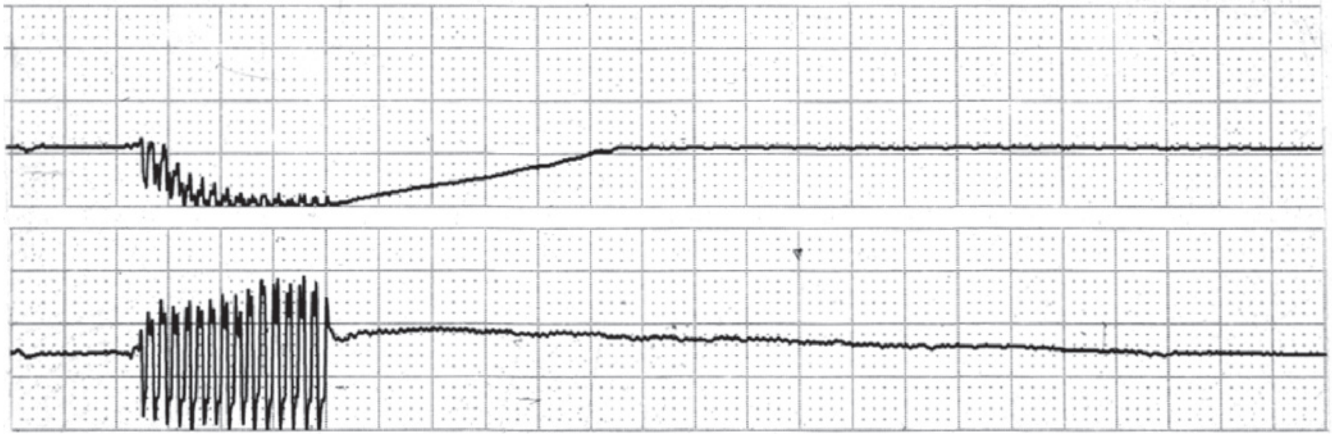


FIGURE 62.3 Simultaneous pressure tracings in the dorsal foot vein and popliteal vein with calf exercise. Note elevation in popliteal pressure and decrease in foot venous pressure after exercise. Popliteal pressure elevation persists for 100 seconds after cessation of exercise before slowly declining to baseline. By permission: J Vasc Surg 2000;1: 631–641.

such as the lateral head of the gastrocnemius or the soleal sling are relatively rare. Compression of the vein by the tibial nerve may occur rarely.

The compressed vein segment often becomes sclerosed and stenotic. Both prestenotic and poststenotic dilatations occur, occasionally large enough to be classified as aneurysms. A thick perivenous fascia attached to the gastrocnemius muscle is an integral part of the compressive mechanism, which may explain the varied location of vein compression noted on venography. The entrapment mechanism likely involves prolonged spasm of the vein initiated by external compression by adjacent muscle. Elevation of the popliteal vein pressure persists long after cessation of active muscle contraction (see Figure 62.3). Entrapment may eventually lead to popliteal valve reflux[2] and perforator incompetence.[20] Unlike in popliteal artery entrapment, anatomic course variations of the popliteal vein are relatively rare.

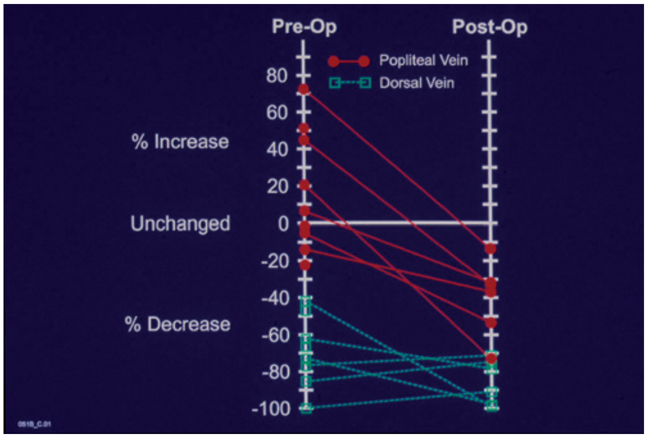


FIGURE 62.4 Elevated popliteal vein pressure after exercise decreases after entrapment lysis. Dorsal vein pressure (post exercise) shows little change. By permission: J Vasc Surg 2000;1:631–641.

SURGICAL TREATMENT

The posterior approach[20] or the medial approach[2] to the popliteal fossa may be used. The posterior approach is preferable if anatomic course variations of the popliteal vasculature are suspected.

The medial head of the gastrocnemius is taken down from the bone with particular attention to the muscle extension beyond the condyle. This extension may be large enough to be described as a third head.[11] As recurrences with reattachment of the muscle can occur, resection of the medial head may be preferable to simple detatchment of the muscle from its origin. Other compressive elements when present should be lysed as well. The vein should be cleared of its perivenous sheath and tributaries over a generous 10 cm length centered on the compressive point. Aneurysmal and stenotic segments should be resected and the vein repaired without any hint of tension using a saphenous graft if necessary. The popliteal valve should be repaired if refluxive, particularly when skin changes are present. Axillary vein transfer may be required if primary valve reconstruction is not possible.[2] Perioperative antithrombotic prophylaxis including use of low molecular weight heparin, meticulous hemostasis, and closed drainage are necessary to achieve clean primary healing without local complications that may predispose to recurrence.

CLINICAL RESULTS

Excellent clinical results with relief of pain, swelling, and stasis skin changes have been reported particularly when the diagnosis is firmly established on the basis of dynamic popliteal vein pressure measurements (see Figure 62.4).[2]

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CHAPTER

63

Valvuloplasty in Primary Venous Insufficiency: Development, Performance, and Long-Term Results

ROBERT L. KISTNER, ELNA MASUDA, and FEDOR LURIE

Widespread interest in the occurrence of deep vein reflux, its clinical effects, the technique of direct valve repair, and the long-term results of valve repair followed the demonstration in 1968 that direct surgical repair of the femoral venous valve was feasible. This chapter will review the background upon which the first repair was based and highlights that have evolved in this field in the 37 years since the first repair.

THE FIRST VALVE REPAIR

The first valve repair[1] was the result of curiosity in a clinical case of swelling, pain, and work disability in a patient who suffered left leg deep vein thrombosis (DVT) following a high voltage electrical burn.

Two years following the injury this patient was unable to return to work due to swelling and pain in the extremity. An ascending venogram revealed the unexpected finding of patency of the entire deep venous system with traces of post-thrombotic scarring in the popliteal vein and the lower thigh portion of the femoral vein. Since this finding did not offer an adequate explanation of the patient's symptoms (swelling above the knee), it was reasoned that the problem was due mainly to reflux rather than obstruction, and this led to the concept of descending venography to determine the valvular status in this extremity. The descending venogram showed full axial reflux of contrast from the common femoral vein (CFV) down through the popliteal vein and into the calf. It also showed a well-formed but incompetent valve at the upper end of the femoral vein (formerly termed the superficial femoral vein). Other valves were identified in the distal femoral vein. Evidence of post-thrombotic scarring in the popliteal and superficial femoral veins was noted.

With the diagnosis of axial reflux as the cause of the patient's symptoms, it was elected to treat the patient after the teachings of Robert Linton[2] by controlling greater saphenous and perforator reflux, followed by control of the deep vein reflux by interrupting the upper end of the femoral vein just distal to the origin of the deep femoral vein in the groin. The patient previously had the saphenous vein stripped. The perforators of the calf were interrupted three days prior to exploration of the femoral vein, and the femoral vein was approached as a separate procedure.

Prior to surgery on the femoral vein, the finding of a normal-appearing valve in the upper femoral vein on the venogram resulted in the decision to explore the valve to see if it might be repairable prior to ligation of the femoral vein. When this exploration at surgery revealed a morphologically normal vein and valve structure with the single finding of elongation of the valve cusp, it was elected to attempt repair of this defect by shortening the leading edge of the two cusps. When this was done the valve appeared normal and it resulted in a totally competent valve upon closure of the vein. It was decided to accept this newly competent femoral valve as replacement for the originally intended ligation of the femoral vein. The patient was managed with full heparinization for the first post-operative week, then switched to Coumadin.

The clinical result was dramatic relief of his symptoms from the first post-operative day when he spontaneously remarked that his leg felt relieved of its congestion. He remained free of unilateral symptoms in this extremity for the remaining 13 years of his life.

This successful surgical repair of an incompetent femoral vein valve in 1968 led to a series of 17 repairs that were the substance of the first national report of the procedure in 1975.[3] This series consisted of advanced venous

insufficiency cases evaluated with ascending and descending venography to identify instances where severe clinical venous insufficiency was associated with axial deep vein reflux rather than deep obstruction.

BACKGROUND KNOWLEDGE OF NONTHROMBOTIC REFLUX DEEP VEIN DISEASE

Except for the publications of Gunnar Bauer in the 1940s,[4] clinically important deep vein reflux disease had been attributed to post-thrombotic disease. Bauer was a brilliant investigator-surgeon who worked in a small hospital in Mariestad, Sweden, in the mid-1900s. He experimented with venography in patients suspected of having venous disease and devised a method of performing descending venography, described in 1948. These venograms were performed with a needle in the CFV and with the patient in the 45-degree erect position. Static films were obtained to document findings. Bauer was the first to report nonthrombotic cases with high-grade axial reflux in the deep veins, and to associate these cases with advanced stages of clinical venous insufficiency. He treated these cases with popliteal vein ligation and reported early clinical success, but later follow-up of some of these cases by his peers in Sweden discredited the long-term value of popliteal vein ligation.

Bauer's descending venography resulted in activity in other sites around the world, as reflected by reports that appeared in the early 1950s.[5,6] Confusion arose from these reports when it was found that deep reflux was associated with symptoms in some cases, whereas other cases were asymptomatic. As a result of this confusion with descending venography and the report that popliteal vein ligation was a questionable procedure, this entity, which had been titled idiopathic nonthrombotic reflux by Bauer, apparently lost credibility as an important cause of venous insufficiency in the 1950s and lay dormant until venous valve repair surfaced in 1975.

The description of the reflux entity that Bauer termed idiopathic nonthrombotic venous insufficiency[4] is identical to the present-day primary venous insufficiency. This entity is fundamentally different than post-thrombotic disease since there is no element of gross inflammation or scarring of the vein or valve, or intraluminal obstruction with wall thickening as found in the post-thrombotic cases.

TREATMENT OF DEEP VEIN REFLUX PRIOR TO 1968

There was great interest in the aggressive management of the chronic venous disease (CVD) leg prior to 1960, which is well summarized in the papers of Robert Linton of Boston from 1938 to 1953.[2,7] Linton refers to the epic work of Homans[8] who drew attention to the importance of the perforator veins and concentrated on the excision of the diseased skin and scar tissue in the lower leg. Homans' understanding of the pathophysiology of CVD is amazing in view of the fact that he had no imaging studies to visualize the leg veins and depended entirely upon clinical acumen to divine the relationship between the skin changes of CVD and the venous system. He came to understand that these changes were related to deep vein disease, which was attributed to post-thrombotic changes in the veins through clinical examination alone. Linton embraced and amplified this thinking and devised a multipronged surgical effort to control venous hypertension by removing the saphenous vein, radically eliminating perforator veins in the calf, ligating the superficial femoral vein, and removing a large segment of deep fascia in the posterior calf to facilitate lymph drainage of the extremity. During the 1950s he was an intense advocate of aggressive surgical treatment for advanced venous insufficiency, essentially all of which he attributed to post-thrombotic venous disease. His papers emphasize the importance of reflux in the genesis of post-thrombotic sequelae as he describes the progression of the originally obstructive thrombosis to a refluxive post-thrombotic state after recanalization of the thrombosed channels has occurred. Although his papers cite the work of Gunnar Bauer there is little or no mention of ascending or descending venography or of nonthrombotic venous reflux disease in Linton's diagnostic workup of the post-phlebitic patients.

EARLY INFLUENCE OF VALVULOPLASTY UPON THE STUDY OF VENOUS DISEASE

The realization that there is an entity of primary reflux disease as a cause of axial reflux separate from post-thrombotic reflux stimulated investigation into the frequency of the two conditions, their diagnostic criteria, and the implications their identification would have upon management.

Among the questions that stimulated the interest of investigators were the need to know the frequency with which axial primary deep vein reflux occurred, the amount of damage it could contribute to the extremity, and the near- and long-term results of its repair. With the ability to repair reflux in the superficial, perforator, and deep veins the concept of total repair of reflux was possible and the question of which conditions would warrant this more aggressive treatment required investigation. For the first time, thorough knowledge of the patho-physiology in each segment of the venous tree had become of practical import because each could be repaired. This ultimately became a strong stimulus to revise the diagnosis of venous insufficiency into an objective image-driven study of the entire deep venous tree.

Some specific questions that stimulated new studies included:

1. What is the pathology of the repairable venous valve? Is it a post-thrombotic valve with minimal damage? Is it a degenerative change in the noninflamed valve? Is it similar to the valve changes in saphenous varicose veins?
2. How often do deep veins develop incompetent valves?
3. Have they been repaired previously?
4. Can they be repaired reliably? How long will a repair last?
5. What are the clinical manifestations of nonthrombotic (pure) deep vein reflux?

These and many other questions led to investigations of advanced venous insufficiency cases that had to be done by venography since noninvasive ultrasound visualization of the veins was not available until the 1980s. Ascending venography was a known and developed test but descending venography was not. Since the early works of Bauer in devising descending venography had lost favor and attention had been focused upon post-thrombotic deep vein disease, new studies with this technique were needed. In the interim, the improvement of fluoroscopic control with dynamic video recording and audio recording of descending venography permitted more definitive descending venograms than were heretofore available. These studies[9,10] resulted in confirmation of the early writings of Gunnar Bauer in which the two causes of deep vein reflux were described. The most important contribution of this newer technology was the ability to trace the dynamic retrograde flow of contrast in refluxing veins and compare this to the normal totally competent systems with well-defined valve outlines. As time progressed, it became possible to distinguish the post-thrombotic diseased valves from the primary valves with a correlation to surgical findings in the range of 90% accuracy.

These reflux studies revealed that the clinical manifestations of CVD reflected by skin complications in the distal lower leg were similar whether the cause was post-thrombotic reflux/obstruction or primary reflux, thereby establishing that the clinical appearance alone is not sufficient to differentiate between these two etiologies. This established with certainty that imaging of the veins in advanced CVD is critical to the accurate diagnosis of the disease process. The importance of differentiating these causes is emphasized because surgical repair techniques and the potential for long-term success are different for the two entities.

Surgical exploration of post-thrombotic cases confirmed that these valves were scarred or completely destroyed in most cases and did not respond well to surgical repair, whereas the valves in primary cases were well-preserved, morphologically normal valves that could be reliably repaired.

The new surgical treatment of primary valve reflux was direct repair of the valve; however, the surgical treatment of post-thrombotic reflux required valve substitution techniques rather than valve repair. Taheri's description[11] (see Figure 63.1) of transplantation of segments of arm veins that contain competent valves into the refluxing segments of the leg where valve destruction had occurred, and the alternative technique of vein transposition[12] (see Figure 63.1), which provided a substitute competent proximal valve in the outflow tract, were devised for use when there were no repairable primary valves available. These procedures were needed for the post-thrombotic limb, but also find useful application in the primary limb when there are no repairable valves.

The question of how many valves are needed to provide clinical compensation to the extremity raised many doubts about repair of a single valve to correct severe venous insufficiency. The teleologic observation that the human has many more valves in the calf veins than in the proximal thigh suggested valves below the popliteal were more important than valves in the thigh, and predicted failure of proximal valve repair. The clinical observations of repaired primary valve cases did not confirm this rationale and has supported a different concept that a single valve interposed into an axial refluxing venous division at the thigh level will be adequate to reverse the clinical syndrome of deep reflux. This was based upon the original reasoning that reflux from the heart to the calf, termed axial reflux, results in sequelae that can be ameliorated by decreasing the incompetent column essentially in half when a single competent valve is placed at the femoral-popliteal level.

When more than one (axial) anatomic division of the veins in the extremity is affected by incompetence, an additional valve is needed for the second division. The axial divisions are several: the usual common femoral-femoral-popliteal-tibial route; the common femoral-profunda-popliteal-tibial route; the common femoral-saphenous-popliteal-tibial route, including perforators; being the main three divisions. If the system contains large collaterals, other routes of atypical axial reflux can develop and need to be identified in individual cases. Eriksson[13] pointed out the importance of different routes of axial reflux when he reported failure in the case of repair of a single competent valve in the femoral vein that was attributed to residual incompetence in the adjacent refluxing profunda-popliteal axial segment. The dilemma of how many valves are needed can be solved by placing one valve in each refluxing axial tract, or by placing a single valve distal to all the refluxing segments, for example, placing a popliteal valve to protect the calf from reflux in both the femoral and the profunda outflow tracts. This location found favor in treating post-thrombotic disease by O'Donnell[14] and Nash[15] with good results.

There have been advocates of providing more than one competent valve per axial segment but none has proven that

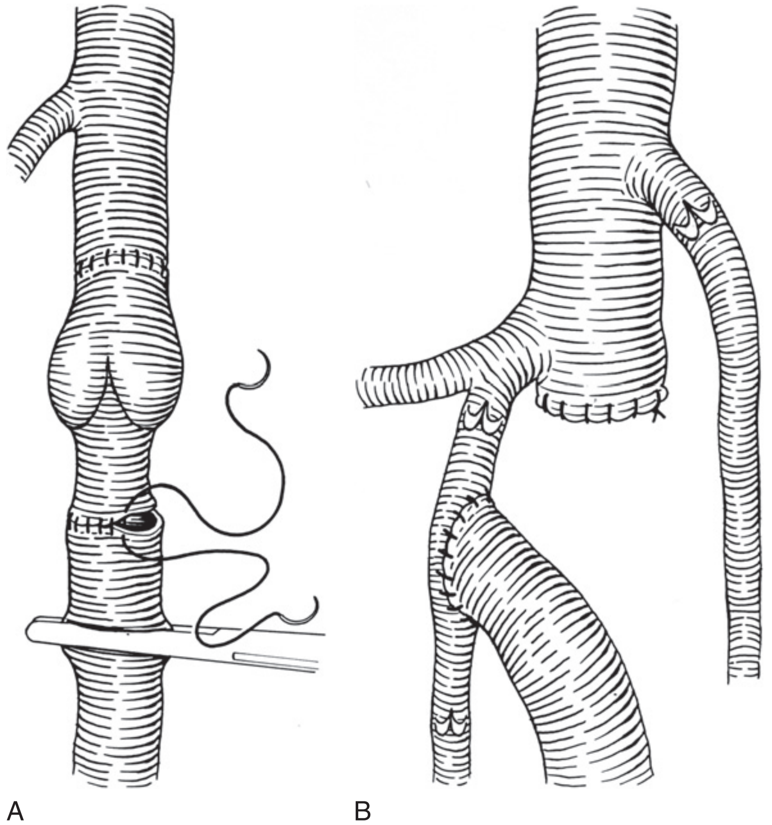


FIGURE 63.1 Valve substitution techniques: **A**. Technique for valve substitution utilizing a harvested vein valve from the upper extremity. The substitute vein was placed end to end in the refluxing vein after the valve had been checked for competency. **B**. Technique of valve substitution utilizing transposition of a refluxing vein to an adjacent vein by end-to-side anastomosis when the recipient vein had a competent proximal and distal valve. The proximal divided end of the transposed vein was oversewn to prevent a potential thrombotic pocket from developing post-operatively.

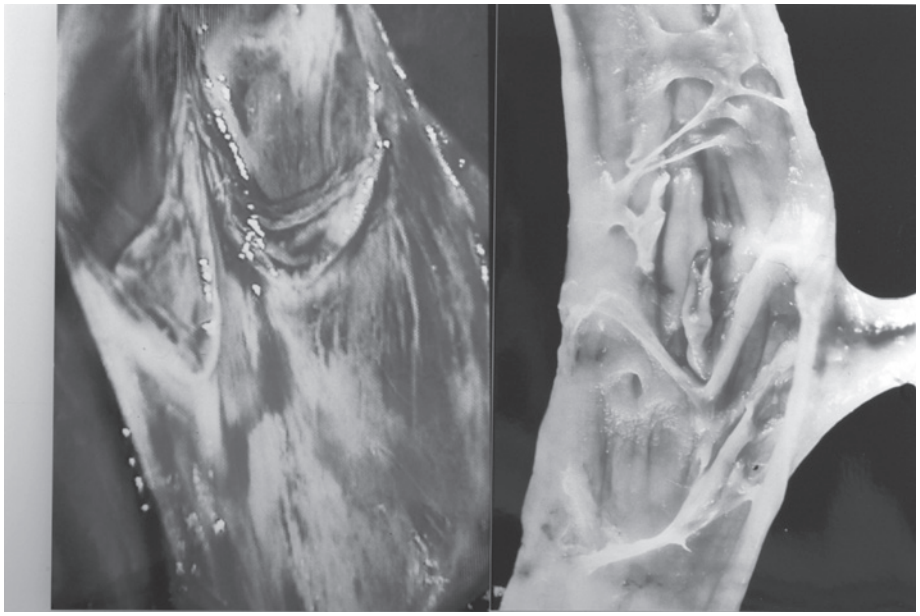
this is necessary. It makes common sense to repair a second valve if one is readily available, but the necessity of repairing a remote valve just to provide a second competent valve in a given axial route has not been widely followed.

PATHOLOGIC CHANGES OF FEMORAL-POPLITEAL VALVES

The difference between the incompetent valves of the primary reflux cases and the valves of the post-thrombotic cases is clear in both gross and microscopic study of these valves. The original description of the gross findings in the morphologically normal valve of primary disease[1] has stood the test of time. These valves are smooth and glistening and delicate, free of synechiae or scars, and surrounded by a normal endothelium in the surrounding vein wall. The abnormality in the primary incompetent deep vein valve is that the free margin of the valve is elongated and the valve cusp lies in folds with sagging margins when exposed at surgery (see Figure 63.2). The endothelial lining of the vein and the consistency of the valve and the vein wall are normal. This is in stark contrast to the grossly deformed valve site of some cases of post-thrombotic disease where the valves are literally destroyed by deforming scars and synechiae and are totally unrepairable (see Figure 63.2), and there is thickening of the wall of the vein.

Within the spectrum of valves exposed at surgery there are some valves that have features of both primary and secondary disease such as a thin valve with smooth endothelium that also has one or more discrete synechiae, or scars, that deform the valve. Since pathologic material is rarely available to study the microscopic aspect of these valves, it may not be clear in a given case whether the valve pathology is truly primary or secondary, or has elements of both. Some have reported long-term success with repairing scarred valves,[16] whereas the Straub experience has been that most of the valves with scarring develop late recurrence following an initial successful repair.

The microscopic difference in the vein wall between primary and secondary valve disease is striking. The microscopic pathology of the primary case involves increase of collagen, decrease of muscularis with entrapment of the muscularis by collagen bundles, and fragmentation of elas-



A B

FIGURE 63.2 **A**. Photograph of a valve with primary venous insufficiency to demonstrate the intima of the vein is healthy and free of scars, the cusp is smooth, thin, and glistening but lies in folds due to elongation of the proximal margin, which presents as sagging edges in the opened vein. **B**. Photograph of a severely distorted, scarred valve site following post-thrombotic changes. This essentially unrecognizable valve site represents a far-advanced stage of the post-thrombotic spectrum and demonstrates the dramatic difference from the primary valve.

tica. This set of conditions would correlate well with loss of tone in the vein wall and lead to dysfunction of the attached venous valve without actually affecting the valve cusp.[17] The typical post-thrombotic changes of inflammatory cells, hemosiderin deposits, and neovascularization are absent. A confounding factor in post-thrombotic cases is that changes of both primary and secondary disease may be present, a finding we interpret to represent inflammatory secondary changes superimposed upon primary degenerative wall changes.

In addition to cases of pure primary insufficiency and of secondary insufficiency, there is a large group of cases with advanced venous insufficiency who have had thrombophlebitis in the calf and popliteal veins, even extending into the lower femoral vein, who also have a refluxing valve in the proximal femoral vein that has all the features of a primary refluxing valve. In these limbs, repair of the proximal valve by valvuloplasty technique yields clinical results and durability of repair that mimics the results of pure primary reflux (see Figure 63.3). This phenomenon of separate areas of post-thrombotic disease and primary disease in the same extremity occurred in the first valve treated by open repair in 1968. Caps has reported finding proximal incompetent valves in his studies of post-thrombotic veins where the proximal valve was distant from the site of thrombosis[18] and reasoned this proximal incompetent valve to be a result of the thrombotic process but lacked prior valve studies to

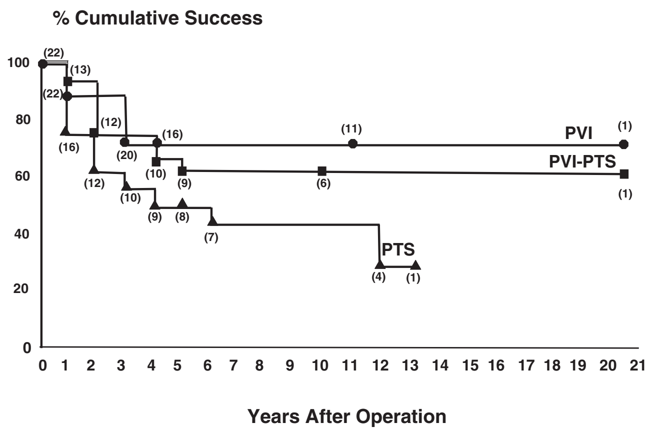


FIGURE 63.3 Life table of results of primary internal repairs (PVI) compared to results after repair for mixed primary and post-thrombotic disease (PVI-PTS) and results after repair for pure post-thrombotic disease (PTS). Clinical criteria for repair were similar for all three groups. Criteria for appearing in this table were that the procedure had been performed 4–21 years prior to this report. The clinical results were superior but comparable for pure primary and mixed primary-secondary groups, but less effective in pure post-thrombotic cases.[19]

substantiate this. Our interpretation has favored the theory that these thin pliant repairable proximal valves are incompetent due to primary disease and were not clinically recognizable until the distal post-thrombotic disease caused axial reflux, rather than attributing them to the phlebitic process.

In either case, this finding of repairable proximal thigh valves in extremities with more distal thrombotic disease is important because up to one third of the repairable valve cases in our series[19] fell into this category.

DISTRIBUTION OF PRIMARY INCOMPETENT VALVES

Primary incompetent veins and valves may occur in segmental or axial distribution. Axial reflux occurs most frequently in the saphenous veins, and often is limited to the saphenous veins in primary disease. The presence of axial reflux in the deep veins is significant in the more serious cases of primary reflux, which present with extensive aching, swelling, and disability.

This distribution of reflux is different than that of post-thrombotic disease where isolated reflux is often found in the deep veins but rarely in the saphenous veins. It is common to find the saphenous vein enlarged and still competent in late post-thrombotic disease, but this would be extremely rare in primary disease. Volume flow studies often indicate the competent great saphenous vein is the major outflow tract in the post-thrombotic extremity when the femoral and profunda veins have prominent elements of obstruction.

In a series of 98 cases of venous ulcers[20] in which the distribution of reflux was studied, the deep veins showed reflux in 73% of cases, perforators in 80%, and saphenous in 86%. The etiologies in these cases were 67% primary and 33% post-thrombotic disease. It is cogent that the deep veins demonstrated axial incompetence in one-third of primary cases and in two-thirds of secondary cases, and the great saphenous veins demonstrated axial incompetence in two-thirds of primary and one-third of post-thrombotic cases. Even in these far-advanced cases of CVD the preponderance of deep vein reflux in post-thrombotic disease contrasts with the preponderance of superficial reflux in the primary cases.

The source of the reflux and wall dilation in primary disease remains controversial between the top-down valvular theory and the contrasting theory that the basic problem begins with degeneration of the vein wall and involves the valves secondarily. Clinical evidence that the initial weakness occurs in the vein wall in primary disease has been presented,[21] and theoretical support for the primacy of wall changes can be deduced from the histologic changes in the vein wall described in the earlier section that described the pathologic changes of femoral-popliteal valves. It is entirely possible that the wall changes result in dysfunction of the valve. Regardless of the initial event, elements of both wall weakness and valvular reflux clearly coexist as the degenerative process of primary disease matures.

The development of primary disease as a progressive phenomenon is well supported by the Bochum investigations,[22] in which young students were followed serially in four-year increments during primary and secondary school and demonstrated progressive reflux in the saphenous and perforator veins, with minimal involvement of the deep veins. This is consistent with the observation that large numbers of early primary cases with varicose veins have no reflux in the deep veins, but progressive involvement beyond the saphenous and into the perforator veins and later into the deep veins is found in patients with more severe degrees of clinical disease as skin changes and ulceration becomes manifest. This contrasts sharply with the natural history of post-thrombotic disease, which nearly always begins in the deep veins and spares the superficial veins.

SURGICAL CONSIDERATIONS ARISING FROM DEEP VEIN REFLUX PATTERNS

The axial reflux patterns of primary deep venous disease must be thoroughly diagnosed prior to planning deep vein valve repair. Primary cases often present with a single axial reflux tract that courses from the CFV through the femoral vein of the thigh to the popliteal and into the calf veins. In this case, a single valve repair in the femoral vein has been shown to be all that is needed to restore clinical compensation to the venous return. These cases usually have little or no communication between the distal profunda veins and the popliteal vein and seldom have other collaterals. The lack of collaterals is due to the lack of an obstructive element in the development of primary disease, in contrast to post-thrombotic deep vein disease.

When the deep femoral vein is incompetent in addition to the femoral vein itself, attention needs to be directed to the distal communications between the profunda veins and the popliteal vein, usually via large connecting branches at the adductor canal (profunda-popliteal connecting veins). If there is significant distal reflux by the CFV-deep femoral-popliteal route, a separate valve is needed for this tract. The choice when reflux occurs by both femoral and deep femoral tracts is either to provide one competent valve at the popliteal level, or two valves, one in the femoral and the other in the profunda veins. In post-thrombotic disease the profunda-popliteal branches provide a collateral route of return flow when the femoral vein itself becomes occluded by the thrombotic process, and it persists when there are elements of relative obstruction in the scarred and recanalized femoral vein outflow tract.

CLINICAL CONTRIBUTIONS TO THE EXPERIENCE OF DEEP VEIN VALVE REPAIR

Following the report of repair of primary venous valve reflux in 1975,[3] a succession of clinical investigators initiated their own case series and developed innovative

technical approaches to valve repair and valve substitution, generating diverse clinical results that resulted in new knowledge about lower extremity reflux disease. Interval reports from the Straub Clinic experience appeared in 1975,[3] 1979,[23] and 1982,[24] describing results of reconstruction in an enlarging group that initially consisted of primary valve repairs and subsequently included post-thrombotic cases; this effort culminated in a four- to 21-year follow-up report of the long-term results of these repairs in 1994.[19]

In 1982 and beyond, widespread reports from other sources presented new developments that have continued until the present. Among the initial publications are a large series of reconstructions for both primary and post-thrombotic disease from the University of Mississippi,[25,26] a smaller series of valve repairs from Sweden[27] with description of the importance of the profunda vein reflux,[13] reports of the Northwestern University experience with transposition procedures,[28,29] report of valve repairs from Boston,[30] and multiple reports of valve substitution procedures beginning with Taheri in 1982[11] and 1986,[31] O'Donnell in Boston 1987,[32] and Nash in Australia 1988.[15] Lane (Australia) in 1988[33] described an external appliance to correct saphenous and femoral vein primary reflux.

Important contributions in the 1990 decade include a new variant in the technique of internal primary valve repair by Sottiurai followed by the initial reports of his series of deep vein reconstructions that has become one of the largest in the world,[34] and description of an angioscopic technique for valve repair by Gloviczki of the Mayo Clinic in 1991[35] supported by confirmatory series from Boston[36] and Japan.[37] DePalma described a type of cross-over study,[38] in which cases with unsuccessful nonsurgical management for advanced venous disease were converted to a surgical approach in 1996 and were followed for comparative control of the venous insufficiency state. In 2001, a well-designed study from Russia reported by Makarova[39] provided a glimpse into the natural history of primary disease and the potential effect deep surgical repair may have upon this progression. Recently, the trap door technique of valve repair was reported by Tripathi in 2001,[40] followed by another large series of medical failure cases that were treated with this surgical repair and followed for two years.[41]

In 1990 a technique for external suture repair of the refluxing valve appeared.[42] The concept of controlling reflux from the outer side of the intact vein by suture or external appliance was found to be appealing because it is simpler, quicker, and safer than internal repair via venotomy. Many variations of the external approach have been developed and enthusiastic reports continue to appear, some of which find comparable results to the open, internal repair. Important reports of enthusiasm for the external approach continue to flow from widely divergent sources, including Asia, Australia, Europe, and the United States, and speak to the desirability of a simple approach to deep vein reflux.

TABLE 63.1 Results of Internal Valvuloplasty

Author	Year	# Limbs	FU mos	Good results	Competent valve
Eriksson	1990	27	6–108	70%	70% @ 4 yrs
Kistner	1994	32	48–252	77%	77% @ 4–15 yrs
Lurie	1997	49	36–108	—	85% @ 5 yrs
Perrin	1997	75	24–96	—	85% @ >1 yr
Raju	1996	68	12–144	76%	76% @ 2–10 yrs
Sottiurai	1997	143	9–168	75%	75% @ >7 yrs
Tripathi	2004	90	24	67%	79% @ 2 yrs

References: Eriksson,[44] Kistner,[19] Lurie,[45] Perrin,[46] Raju,[47] Sottiurai,[48] Tripathi.[41]

The fundamental difference between the internal and the external repairs is that the internal repair provides anatomically precise correction of the elongated leading edge of the valve cusp, and the external repair acts by altering the vein from the outside in one fashion or another and is not a precise correction of the valve cusp abnormality. Some believe the external repair can be performed in a manner to achieve the correction of the elongated valve cusp, but the evidence that this truly occurs lacks precision. Theoretical support for the concept of narrowing the base of the valve and deepening the valve pocket with the external repair is imaginable and if the long-term results can be proven comparable or better than the internal repair this would become the procedure of choice. At this time, though, the better results continue to follow open repair in the hands of those who are facile with both approaches. The overall statistics for long-term (>4 years) competence of the repaired valves lie in the range of 65 to 85% for internal repairs (see Table 63.1) compared to ranges of 50 to 65% for external repairs. In spite of this difference, situations when the external repair may be a better choice occur when technical or risk factors render the internal repair a more risky procedure than the surgeon may wish to undertake even though the internal repair carries a higher long-term competence rate.

INFLUENCE EXERTED BY THESE MULTIPLE REPORTS

As these reports developed, new knowledge emerged about CVD that was discovered through an intimate relationship between improved diagnostics coupled with direct knowledge of the venous pathology derived from open surgery on the veins themselves. Points such as the following emerged:

1. Identical clinical presentations can develop from pure primary reflux to those seen in the reflux-obstructive changes of post-thrombotic disease. This meant that definitive diagnosis (sufficient for surgical treatment)

would have to be done by objective imaging techniques.

2. The practical importance of differentiating primary from secondary deep vein disease was established to permit deep venous surgical correction.
3. Global testing (venous pressures and much of plethysmography) has been replaced for practical value by more specific ultrasound imaging.
4. Results of treatment protocols began to be evaluated by noninvasive techniques, of which imaging has been the most specific.
5. Multiple approaches to repair of deep vein reflux in both primary and post-thrombotic disease emerged from around the world.
6. The need for definitive diagnosis of the cause and distribution of segmental vein disease played an important role in stimulating the later development of the CEAP classification of chronic venous disease in 1994.[43]

INFLUENCE OF DEEP REPAIR ON MANAGEMENT OF CVD

With the definitive workup of all the vein segments mandated by the ability to repair reflux throughout the extremity in patients with advanced disease, clinical correlations between disease states and pathologic findings assumed increasing importance. Correction of axial superficial and deep reflux in all the patients who are symptomatic was not found reasonable because there are mildly symptomatic and even asymptomatic patients who have significant deep reflux in whom development of long-term serious sequelae has not been proven.

The initial aggressive surgical approach of repairing the deep system in those with advanced (C4–C6) disease who had not responded to medical therapy, the so-called total surgical repair of reflux in advanced cases, led to the criticism that many cases could probably be controlled for a significant period of time with lesser procedures limited to saphenous and perforator veins even though deep vein reflux persisted. This has been found to be true and resulted in a more conservative surgical approach that reserves deep vein reconstruction to cases that demonstrate failure of both medical and conventional saphenous and perforator surgery. Most of the series that have been reported in the past two decades have reportedly followed this concept[19,41,44–48] but the absence of criteria for adequate medical therapy, as well as provisions of satisfactory surgical treatment of saphenous and perforator veins, have resulted in the likelihood of considerable variability in case selection between the reports in the literature. Suffice it to say that the surgical selection of patients for deep repair has been largely restricted to resistant cases with serious manifestations of CVD who have not responded to initial efforts to control their problem by simpler methods up to the time of surgery.

For the surgeon and clinician, the clinical experience of the effect of placing a competent valve in the extremity of a patient with advanced primary disease is dramatic. Time and again the patient will recognize an immediate sense that the extremity is more comfortable. If an ulcer is present, a period of accelerated healing follows the successful repair. Improvement of C4 changes in the extremity become dramatic over the next several weeks to months. Over the course of months to years, the far-advanced changes of leathery dark skin may improve to soft skin and subcutaneous tissue with near-normal texture and turgor. The dark color of late-stage pigmentation can lighten considerably, although it rarely disappears entirely. Swelling will entirely disappear in some cases, but others retain an enlarged extremity that may or may not swell on a daily basis. For those who observe these favorable events after correction of deep vein reflux, there is no doubt about the import of deep vein reflux on the deranged physiology of advanced venous insufficiency. This phenomenon of clinical improvement after elimination of deep reflux is not new, having been mentioned by Homans, Linton, Bauer, and others after interruption of refluxing femoral or popliteal veins, which produced more temporary relief of symptoms.

A concept was advanced that repair of superficial reflux resulted in a decrease or disappearance of deep vein reflux in a high proportion of cases.[49] This concept supports the realization that axial deep reflux at times is a reflection of the interdependence of the superficial and deep segments of venous return. One study focused on the effect of ablation of superficial reflux in the presence of deep segmental vs. axial reflux and concluded that the abolition of deep reflux by superficial ablation is unlikely when actual valvular deformity is present.[50] The knowledge that deep reflux may be decreased or eliminated by saphenous and perforator surgery reinforces the concept of initial repair in these veins prior to deep repair.

SURGICAL CONSIDERATIONS IN REPAIR OF PRIMARY DEEP VEIN REFLUX DISEASE

Practical questions that face the surgeon who will repair the deep vein reflux in primary disease include which vein to repair, the exact site of repair, and which surgical technique to employ.

Preoperative Evaluation

Good surgical results begin with accurate diagnosis of the venous problem. The goal of the preoperative evaluation for deep vein reconstruction is to identify sites of both reflux and obstruction in all the venous segments from the inferior

vena cava to the calf. This task is readily achieved with the aid of expert duplex scanning and venographic techniques.

It is incumbent upon the surgeon who undertakes deep vein reconstruction to have expert scanning available to guide his choices at all stages of diagnosis and follow-up. The minimal requirements of the ultrasonographer should include experience in identification of reflux and obstruction in all the venous segments, ability to identify hemodynamically important tributaries of major veins and collateral flow routes, and most important, the capacity to individualize the scanning protocol to identify the anatomically and physiologically unique variations that occur in advanced venous disease. Since the knowledge of flow routes in CVD is still evolving, the ultrasonographer should have sufficient background to contribute to this progress as an essential member of the venous team.

With the advent of improving technology and technique in duplex scanning, the need for venography has been materially lessened over time for pure diagnostic purposes, but ascending and descending venography continue to be very helpful in planning deep vein surgical procedures.

Ascending venography provides a map of the physiologically preferred route of venous return from the foot when it is done in the erect position without tourniquets. When it shows deep return via the tibial, popliteal, and femoral vein without filling collaterals, one can deduce there is no important deep vein obstructive disease. Conversely, when it shows collateral patterns it is incumbent upon the surgeon to search out and understand where the obstructive elements are located in the normal deep vein return vessels to produce these collaterals. In this way, both gross and subtle degrees of obstructive changes can be ferreted out and subtle elements of post-thrombotic change can be detected. When collaterals are being studied, liberal use of tourniquets at the ankle, upper calf, and lower thigh may demonstrate filling of partially obstructed veins that had been bypassed by the ascending contrast because these veins presented higher resistance to outflow than the collateral routes.

Descending venography provides a map of the location of deep vein valves and a measure of their competence when performed with adherence to the details of the reported technique for detecting valve function.[10] It is best done with the treating surgeon in direct consultation with the radiologist at the time of the procedure in order to achieve optimal understanding of the morphology and the relative degree of competence and operability of the individual valves. This test should always include audio and video recording in order to be able to interpret the data on the film at future times. Catheter techniques allow for selective study of the femoral, profunda, saphenous, popliteal, and tibial veins. The x-ray table should move from the Trendelenburg to the erect position mechanically to take advantage of the effects of gravity upon the venous flow in the standing position, and to be able to empty residual contrast from the veins by sharp Trendelenburg positioning.

The information gained from venography should be compared to the duplex scan data because they provide complementary information in most instances and, when there are differences between the studies, repetition of the scanning after venography will often provide clarification of important, even crucial, details.

Physiologic Noninvasive Testing

The use of pressures and plethysmography in evaluation of the patient for surgery can be helpful in confirming that there is significant venous disease, but is seldom helpful in determining critical details of the preoperative workup. These tests are global in nature, especially the venous pressure test, and for this reason it can be used on a highly selective basis. Plethysmography provides more detail and is more practical than venous pressure, especially the VFI (venous filling index), which provides a measure of the reflux in the veins when the extremity is inverted. It has been related to the severity of venous insufficiency and certain centers use this test as an important part of their estimation of severity of reflux in CVD and in reconstruction.[51]

Preoperative Planning: Choice of Surgical Technique and Placement of the Competent Valve

In planning the surgical approach the surgeon must decide which valve(s) to repair and which technique to use for the repair. The choice of the valve is dictated by the imaging studies, which show the axial refluxing segments and the location of the valves within these segments. There is no good evidence that repair of a valve above the femoral or profunda level is physiologically effective, but abundant evidence exists to support the finding that repair below the common femoral level is effective. The first point to ascertain is whether the reflux is limited to one or more axial distributions (femoral-popliteal-tibial vs profunda-popliteal-tibial vs saphenous) from the groin to the calf because each of these routes of reflux require at least one competent valve. When more than one valve in a segment is readily available for repair, it is opportune to repair the additional valve. When there is reflux in both femoral and profunda veins, placement of a single valve in the popliteal vein will control both routes of reflux; otherwise, at least one valve for each of the refluxing segments should be provided.

The choices for technique of repair are multiple. The first choice is whether to plan an internal or external repair. The internal repairs are the most reliable and durable, but

external repairs are simpler and safer because the vein does not have to be opened. In the good risk patient with a valve that appears favorable for the internal approach, it would be a logical choice to plan an internal repair. If it is a less favorable case by reason of surgical risk or anatomical exposure, as in an obese subject or an anatomically difficult position of the valve, the external repair may be preferable.

The internal repair can be done by any of several techniques as discussed earlier. Since the follow-up statistics for valve competence are similar between the transvalvular[19] (see Figure 63.4), supravalvular,[47] and T-incision exposures,[48] the choice of technique is a matter of the surgeon's preference. If the surgeon has the technical facility, the angioscopic technique[35] is reasonable.

The external repair[52] (see Figure 63.5) of the deep valve has been well received by many surgeons. The significant advantages are that external repair is a simpler operation with less risk of complications because it does not require opening the vein and carries a very low likelihood of postoperative thrombosis, especially in the non-post-thrombotic patient. Heparin is not needed, which minimizes the chance for significant wound hematoma. The problem with the external repairs is that the long-term results are not as good as the internal repair in most reports. The expectation for long-term competence with external repair has been about 50% in the author's Straub Clinic experience compared to more than 70% competence with internal repair. Other centers have found the external repair results to be more comparable but still not equal to the internal repair.[48,53] The use of external repair can be valuable when the repair is made difficult due to a deeply placed valve with limited exposure, or in the repair of a second valve to supplement an internal repair.[42] There are sizable reports of external circumferential suture repairs from Chinese,[54] Japanese,[55] and Italian[56] authors.

At this time, the summary statement for choice of surgical approach is that the internal repair provides an exact anatomical correction of the primary defect of elongation of the valve cusp, has produced the best results, and remains the procedure of choice for long-term results. When there are circumstances such as the need for a limited procedure or a difficult exposure, one of the exterior techniques may become the better alternative. In the primary case where there are no repairable valves one of the valve substitution techniques of transposition or transplantation of a valve-bearing arm segment can be used.

Regardless of technique, the principle is well demonstrated that restoration of competence to the lower extremity affected by primary axial reflux disease can effectively reverse advanced CVD even when this has been refractory to best medical therapy and to repair of saphenous and perforator reflux. The durability of the internal repair has been established, as cited in Table 63.1. Even in the absence of Grade I evidence based upon prospective randomized trials, the collective clinical benefits of surgical reversal of extensive reflux are clear in the literature.

PUBLISHED RESULTS OF PRIMARY DEEP VEIN VALVE REPAIR

There are abundant data in the individual case series that advanced CVD resistant to more conventional measures of medical management and saphenous-perforator repair provides relief of pain, swelling, disability, and is followed by a marked improvement in the recurrence rate of ulceration and debilitating skin changes.[19,32,38,41,44–46] These reports consistently demonstrate that resistant cases of advanced CVD due to primary reflux experience clinical relief of recurrent ulceration and skin changes in the range of 65 to 80% for periods that exceed four- to eight-year follow-up (see Table 63.1). The results for clinical relief following repair of post-thrombotic reflux and obstruction (in the range of 40–65%) are less favorable than the primary reports but represent significant salvage rates in cases that are otherwise committed to progressive disability and discomfort. This is understandable since post-thrombotic disease is a more destructive and complicated problem because it reflects post-inflammatory destruction of the vein wall and lumen and encompasses elements of obstruction in addition to the reflux, whereas primary disease is noninflammatory and degenerative in nature, and is restricted to the effects of reflux without morphologic obstruction.

The first presentation of truly long-term results (4–21 years) in 1994[19] provided initial data that cases with open repair of primary refluxing valves had a 73% chance of very long-term (>10 years) recurrence-free clinical improvement in the case of pure primary reflux, and 66% when the problem consisted of distal post-thrombotic disease and proximal femoral vein primary valve disease. In all these cases the limb remained free of recurrence of the C4–C6 skin changes that constituted the indication for the operation. Similar results over four to eight years, and beyond, have been presented by multiple other surgical series[19,45–48] that provide reproducibility for the original report. At least 30% of cases have voluntarily discarded elastic support against medical advice in several of these series and still remained free of recurrence over the long term. This result has never been reported with medical management and speaks to the critical importance of correction of deep vein reflux.

There has not been a randomized prospective trial of medical vs superficial surgery (saphenous and perforator repair) vs deep surgery. The wide variation in pathologic findings of advanced CVD cases would render it a difficult task to accumulate exactly similar cases. Lacking this, the collected data of multiple individual carefully conducted studies with similar results provides impressive repeatable

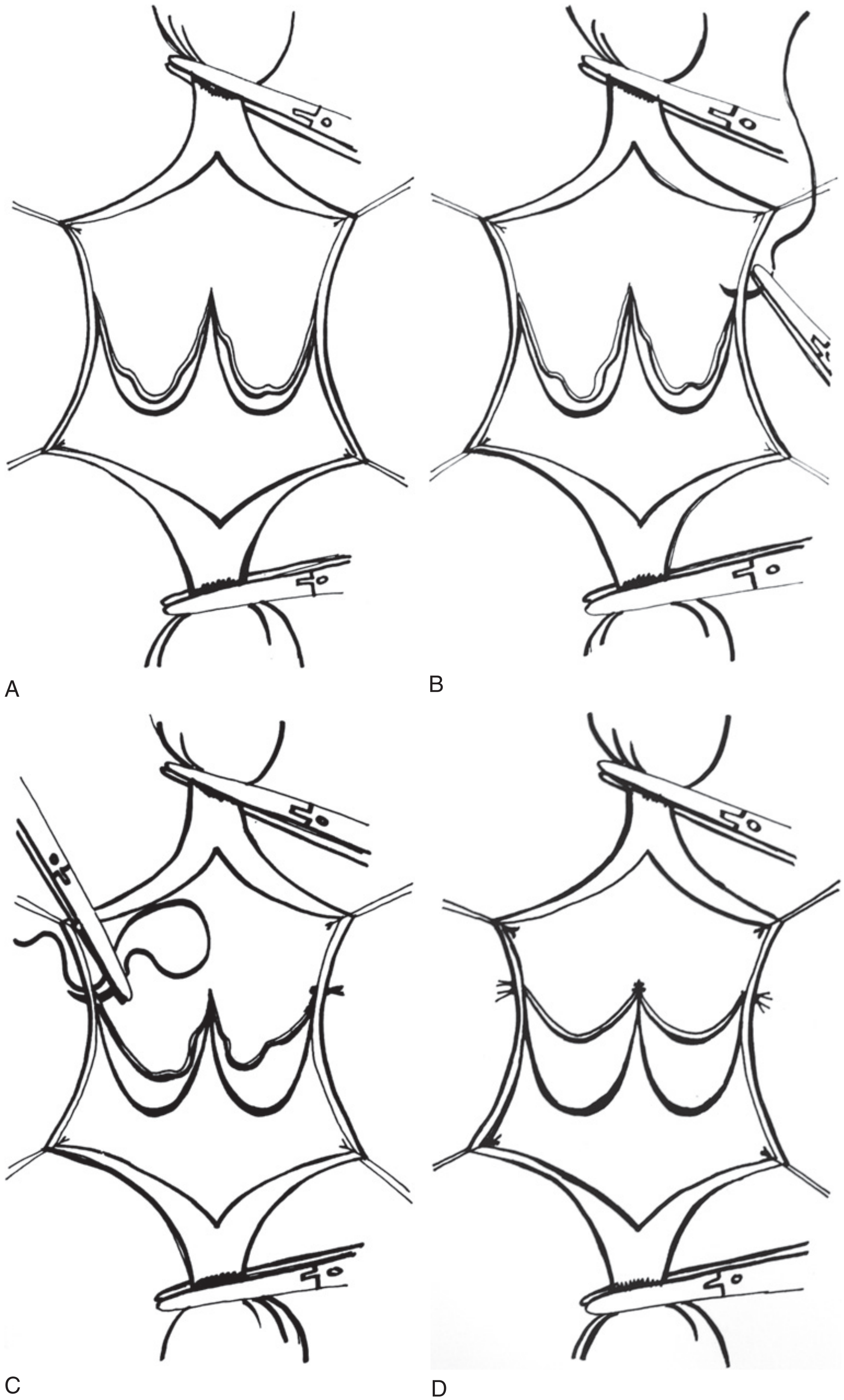


FIGURE 63.4 Original transvalvular technique of internal valve repair. **A**. Diagrammatic appearance of sagging valve cusps as seen in the opened vein prerepair. **B**. Technique of shortening the leading edge of the valve cusp for 2–3 mm distance with interrupted 7–0 monofilament suture introduced at the level of the commissure passing from outside to inside the vein, through the cusp near its leading edge, then returned to the level of the commissure and passing from inside to outside of the vein. **C**. Introducing further similarly placed sutures, which will be done at both sides of the opened vein and in the center of the vein where both valves meet. **D**. Appearance of valve cusps after shortening the cusps to an appropriate length. This may require 4–10 such sutures.

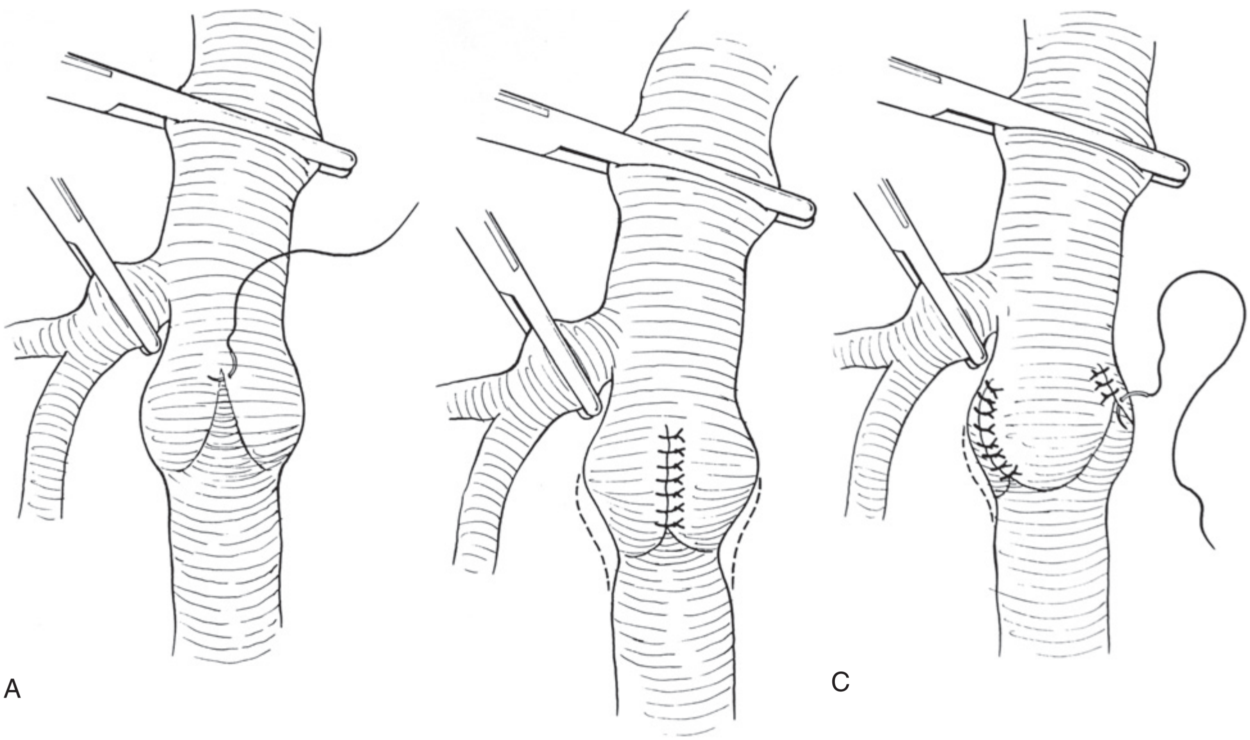


FIGURE 63.5 Original technique of external valve repair. **A**. Interrupted sutures begin at the upper level of the commissure where the valve cusps originate. The suture passes into the vein from the outside to the inside to engage the valve cusps and is tied outside of the vein. **B**. A series of similarly placed sutures passing down the valve secure the progressively decussating margin of the valve insertions until the base of the valve is reached. **C**. Similarly placed sutures are then placed along the margins of the cusps on the opposite side of the vein.

evidence (Level C) for validity to this approach to advanced primary venous reflux disease.

PERSPECTIVE ON THE VALUE OF SURGICAL REPAIR IN DEEP VEIN VALVES

Caution is advised when comparing reports of nonsurgical treatment of deep reflux to those of deep surgical repair. There is a cogent difference between the cases in the surgical versus those in the nonsurgical reports of management for advanced CVD because the nonsurgical group has little definitive workup including a lack of detail about primary versus secondary disease and the extent of reflux or obstruction in the venous segments. In many instances the medically treated series are a mixture of first-time ulcers and recalcitrant ulcers, and the endpoint is the first healing of the ulcer. Data about recurrence of disease often are lacking. These reports lack the specificity of the reports of surgical deep repairs, all of which have been extensively evaluated to determine the etiology and the entire distribution of disease throughout the extremity and the recurrence rates are carefully traced. Since the surgical cases are nearly all resistant cases that have failed both medical management and surgical repair of superficial and perforator incompetence, the recurrence rate of ulcer and skin complications in these cases would be expected to be high and soon unless some correction had been done or some dramatic change in their way of life had occurred.

COMPLICATIONS OF DEEP VENOUS VALVE REPAIR

The complications of deep vein repair are primarily wound hematoma and deep vein thrombosis. Since the operation is performed under preoperative heparin and the heparin usually is continued post-operatively, there is increased opportunity for a wound hematoma to develop. If large enough, a wound hematoma can compromise an otherwise successful repair through local pressure and thrombosis of the venous segment. The frequency of this can be minimized by limiting the heparin dose to 400 to 800 units of heparin per hour for the first two post-operative days and by draining the wound with continuous wound suction

with early surgical wound reexploration if bleeding is found in the first post-operative days.

Post-operative deep vein thrombosis is infrequent following open surgery for primary disease (incidence unknown, approximately 1–3%), but more frequent when the disease is post-thrombotic or the patient is hypercoagulable. Since the potential for thrombosis is present, heparin has been recommended preoperatively and for the first four to seven post-operative days until the patient is ambulatory and the wound is healing well without hematoma. If there is an element of post-thrombotic disease in the patient, or other reason for hypercoagulability, heparin can be followed by Coumadin anticoagulation for weeks or indefinitely.

If the external repair is elected, the chance for DVT is virtually eliminated in the absence of hypercoagulability. When the underlying problem is mixed primary and post-thrombotic disease it is wise to use aggressive heparin to prevent post-operative thrombosis that could result in transforming an original primary venous problem to a post-thrombotic problem.

Post-operative thigh swelling is seen in some cases probably due to lymphatic disruption from the surgical dissection. This will generally clear in about six weeks. Transfusions are rarely needed for this kind of surgery. Infections are unusual because it is a clean operation.

CONCLUSION

Surgical repair of deep vein valves for primary disease has been widely evaluated and found to have reproducible favorable results without recurrence in 65 to 80% of cases successfully operated upon with internal repair. The repair can be performed in many different ways with the best long-term results achieved by open surgery, but with higher risk for complications after the open techniques than after the external techniques. Its use can be recommended in resistant CVD cases in which a repairable valve is identified.

In addition to pure primary disease, repairable valves can be found in the high thigh veins in a number of cases with distal deep vein thrombophlebitis when the more proximal valve(s) has been spared inflammatory involvement.

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C H A P T E R

64

Prosthetic Venous Valves

MICHAEL C. DALSING

INTRODUCTION

The need for a prosthetic venous valve in the treatment of chronic deep venous valvular incompetence (CDVVI) or insufficiency becomes evident only after other options have failed or simply are not practical. The typical patient has end-stage chronic deep venous insufficiency afflicted with acute and/or recurrent venous ulceration resistant to standard medical therapy, has exhausted all superficial/perforator surgery that might be helpful, and has no autogenous venous valve available to use in the correction of the deep venous disease. In some cases, less advanced cases are considered for intervention because of severe lifestyle limiting concerns. These patients generally have post-thrombotic disease that often renders the deep veins thickened and scarred yet recanalized resulting in unrelenting reflux while standing. The stiff, thickened, noncompliant vein makes intervention more difficult than in the case of primary insufficiency. These, our most challenging patients with venous disease, often are the most symptomatic and therefore any attempt to remedy the condition may result in a less impressive outcome than in other patient cohorts.

For the current discussion, the term "prosthetic" means dealing with the production or use of artificial body parts and the term "artificial" means not arising from natural growth. Therefore, a prosthetic venous valve is any venous valve substitute not originally arising from the recipient as a *de novo* venous valve. This eliminates consideration of autotransplantation, or valve transposition procedures. All other options are considered and generally fall into two categories: *Scaffold seeks incorporation as self after implantation* or *Scaffolds identified as self prior to implantation*. The quest for a minimally invasive venous valve implant will also be addressed since it lends itself to some prosthetic valves and is certainly a desirable approach in the view of most patients.

DATA

Scaffold Seeks Incorporation as Self after Implantation

Over the last few decades, several potential off-the-shelf implantable valves have been tested as a substitute for the autogenous venous valve. The valves may be allografts, xenografts, or synthetic in design.

Animal Studied/Poor Results

Transplantation of a fresh vein containing a valve from one canine to another without concern for rejection issues has been attempted. Of 14 fresh allografts tested, utilizing 24 hours of initial anticoagulation to boost patency, only 7% were patent and none competent over a four-week study period.[1] Glutaraldehyde-preserved allografts, even when supported by a continuously functioning distal arteriovenous fistula (dAVF), would remain patent (80%) but rarely competent (25%) in the dog during a seven-week study.[2]

Xenograft transplantation initially was investigated using human umbilical vein that could be frozen, cleaned, fitted over an aluminum mandrel, and finally fixed with glutaraldehyde to sculpture a bicuspid valve for implantation.[3] The recipient was canine and all 10 transplants failed in three days both in terms of patency and competency. This experiment was unique in that the valve structure itself was not made in nature.

Completely synthetic designs also have been investigated. Using the same aluminum rod design to fashion a bicuspid valve with umbilical vein, liquid pellethane was made into a valve. All 10 canine implanted valves thrombosed in eight days.[3]

Animal Studied/Some Potential

Platinum or pyrite-carbon covered titanium center-hinged bileaflet valves have been implanted into the femoral vein of three dogs.[4] Initial results demonstrated 100% patency and competency at approximately three months.[4] At two years, the valves demonstrated extensive neointimal hyperplastic ingrowth, which rendered the valves nonfunctional.[5] Although a long-term negative study in the canine model, these results do hold some promise that modification could extend the life of the valve sufficiently to be clinically useful.

Decellularization of venous valved allografts could provide a transplant devoid of the immunologic impact of donor cells. An early clinical experience with a cryopreserved decellularized allograft when used as a conduit for an arteriovenous fistula (AVF) appeared promising and incited very little antigenic response as determined by PRA (panel reactive antibody) levels.[6] This material, when used as a heart valve, demonstrated a similar lack of antigenic response and acceptable valve function.[7] However, a decellularized external jugular vein containing valve allograft when implanted into the venous system of a recipient sheep and without supportive anticoagulation demonstrated a 100% (4 of 4 tested) occlusion rate at six weeks.[8] Although the only animal study using a decellularized venous valve allograft in the venous system had a negative conclusion, some clinical data using this material in other settings would suggest the need for further study.

Allografts of lyophilized vein containing a valve have been mechanically tested following rehydration with valve response much as one would observe in a native valve.[9] The valve cusps could withstand at least 350 mmHg retrograde pressure without rupture or insufficiency and the valve closure time was an acceptable 0.31 ± 0.03 seconds. This allograft is totally untested as a potential venous valve substitute; there are no animal or clinical trials reported.

Fully Studied/Unsuccessful

The only allograft valve to reach clinical study involved standard allogenic cross matching and cryopreservation as the storage process. Dog eurythrocyte antigen (DEA) matched and cryopreserved vein containing valve allografts have been transplanted into recipient dogs with preestablished lower limb venous insufficiency. Following ligation of a high flow dAVF that had functioned for three to six weeks, all four transplants remained patent and competent for three more weeks, at which time the animals were sacrificed for histologic evaluation.[10] The histology appeared very promising with what appeared to be endothelial cells present on the luminal surface and devoid of thrombus in the cusp sinuses (see Figure 64.1). From this study sprang the initial multicenter feasibility evaluation, which unfortunately suggested that a low grade rejection phenomenon might be affecting the function of the valve transplants.[11] The primary patency rate was 67% and primary competency rate 56% at six months. A two-year clinical study evaluating 27 cryovalves reported a disappointing 27% patency and competency rate.[12] The cyropreserved valve allograft used in this study has failed early and in midterm clinical trial is no longer considered a viable substitute for the native valve in the treatment of CDVVI.

Glutaraldehyde-preserved bovine tissues have been used with success in cardiac surgery and the technology exists to construct glutaraldehyde-preserved bovine venous valves of appropriate size for use in the lower leg of humans. Furthermore, the possibility of valve transplantation via a percutaneous route has been demonstrated to be feasible experimentally.[13] A percutaneously placed glutaraldehyde-preserved bovine venous segment with a contained valve demonstrated acceptable early results in the swine model.[14] At two weeks, the xenograft was patent and competent in the three surviving animals. This and other unpublished data were sufficiently compelling to begin clinical trials, but early clinical thrombosis with this particular experimental design was discouraging. A streamlined design was constructed (personal communication) but the new design may not have solved the clinical problem since the company that investigated this valve is no longer in existence.

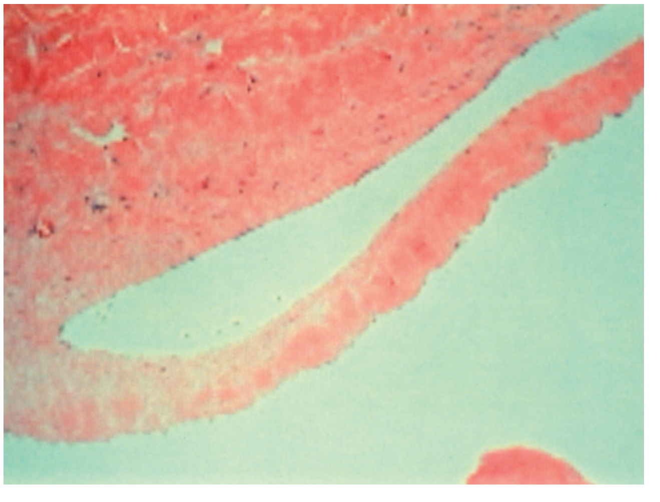
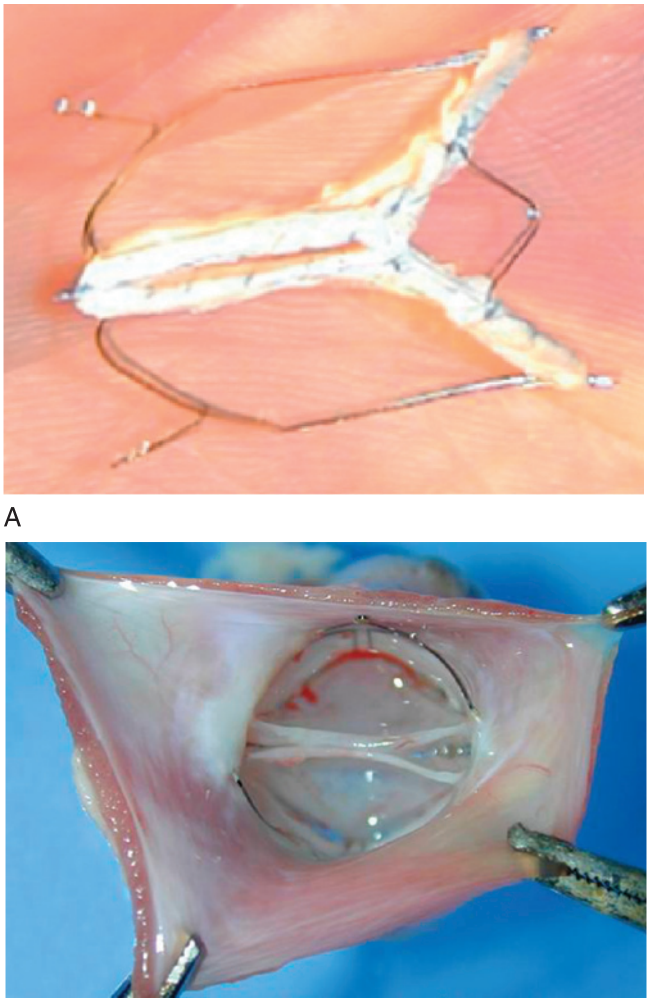


FIGURE 64.1 This photomicrograph shows a cryopreserved venous valve after removal from an animal model of CDVVI. Note the cellular lining of the valve cusp and minimal thickening.

Clinically Unavailable/Unstudied

Most recently, a bioprosthetic, bicuspid square stent-based venous valve has been developed and percutaneously placed in the external jugular vein of sheep in a feasibility study.[15] The valve is made of processed small intestinal submucosa (SIS) (essentially collagen with growth factors remaining) stretched between a square metal frame with a slit cut in the middle of the SIS sheet to form the valve opening. The valve appears to be relatively resistant to thrombosis and does become repopulated with recipient endothelial cells following implantation.[15,16] When percutaneously deployed in the sheep external jugular vein, it demonstrated an 88% patency and competency rate but tilting led to occlusion or valve insufficiency in three experimental animals.[15] This observation led to a design change to prevent misalignment within the vein wall and six of eight valves were competent at five weeks of study.[17] The company sponsoring the study of this valve (Cook, Inc., Bloomington, Indiana) confirms that the device is in research and development with some early clinical studies performed outside the United States. A third design change has taken place to improve venous hemodynamics around the valve cusps and thereby to prevent cusp thickening (see Figure 64.2 A,B).



A

B

FIGURE 64.2 **A**. This is the newest redesign of the SIS or Portland venous valve aimed at preventing tilting and to provide for a longer cusp, which is suggested to be a more hemodynamic structure. It was photographed from the side. **B**. This is a SIS valve cusp photographed from the top to demonstrate the valve opening more clearly and to show its delicate structure. (With permission: Dr. Susan Pavenik.)

Clinically Available/Unstudied

A cryopreserved superficial femoral vein containing valve allograft (cryovalve) remains available from the CryoLife company (CryoLife, Inc, Kennesaw, Georgia). It will maintain valve competency to 125 mmHg of tested retrograde valve pressure. It may require primary valvuplasty post-thaw for optimal competency at the time of implant.[12] Without modification, it does not perform adequately to be recommended for the long-term treatment of patients with CDVVI but, if one could potentially modify the apparent rejection issues faced by the valve substitute, it might be useful.[11,12] The immunosuppression would have to be minimal, well-tolerated, and not risk systemic infection since the standard patient with a venous ulcer is not systemically infected but certainly does possess a port for potential infection. Cytotoxic T-cells to foreign endothelium may be the primary cause of rejection such that azathioprine or cyclosporine A would be potential immunosuppressive agents to consider. There are no clinical trials available investigating such a modified protocol for the use of the cryovalve in the treatment of CDVVI.

Scaffolds Identified as Self Prior to Implanation

Animal Studied/Some Potential

A venous valve can be made from a length of vein in the fashion of Eiseman and Malette. The basic technique involves an intussusception of the vein into itself with an appropriate bicuspid valve made by two sutures placed at 180 degrees from each other to hold the inner vein wall in the correct position.[18,19] The base tissue is autogenous vein but the valve structure would be artificial since the vein tissue used is not a natural valve cusp. In the experimental studies, only operative heparinization was administered and no long-term anticoagulation was provided to the animals. Short-term patency was excellent with 90 to 100% of valves competent at physiologic pressures. The valve was certainly thicker than the native valve on gross and histologic study (see Figure 64.3).[18] However, when used in a chronic lower limb deep venous insufficiency canine model and transplanted to the femoral vein, the 90% venous refill time was

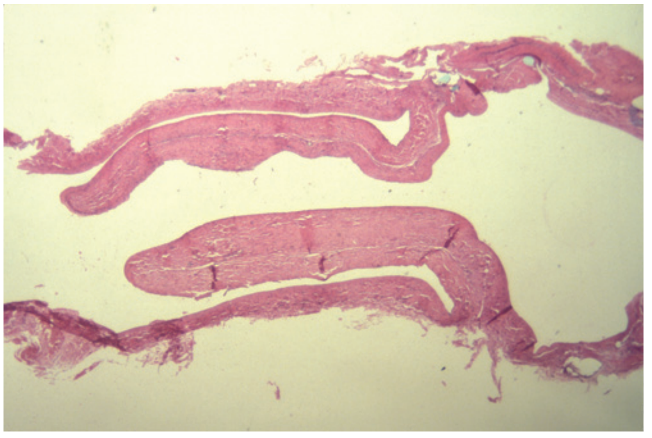


FIGURE 64.3 This photomicrograph shows that the invaginated vein valve design (Eiseman/Mallete design) results in a thicker valve than a normal venous valve even several weeks following implantation in a canine model.

modestly improved but not the venous filling time, which suggested that the valve was not as hemodynamically responsive as a native valve.[18] A modification of this valve involved thinning the adventia and a part of the media to result in a thinner valve cusp after intusseption and it has been investigated experimentally in the canine model.[20] The valve opened rapidly with minimal pressure (<3 cm of water) and closed at a pressure of 3 to 5 cm of water. Furthermore, it could withstand physiologic pressure without reflux. In the absence of prolonged anticoagulation, a thin layer of thrombus formed along the cusp wall resulting in valve incompetence. These studies suggested that such valves constructed of autogenous vein could function as a substitute of the native valve with the caution that these valves may be more prone to thrombosis and possibly less responsive in a hemodynamic sense than a native valve. No clinical trials have blossomed from these experimental studies possibly because a significant length of vein is required for its construction and patients with CDVVI often have little to spare.

Repopulating a decellularized external vein containing valve allograft with donor smooth muscle cells and endothelial cells would make for a transplant quite similar to an autogenous valve. One author has studied this approach in a sheep model with quite excellent results. The seeded allograft was transplanted into the external jugular vein of the sheep that provided the cells for seeding. Without the use of anticoagulation, nine of 12 seeded allograft transplants (75%) were patent and competent at 12 weeks. One transplant had occluded and two others had valves frozen in the extracellular matrix of neointimal ingrowth.[8] The technique seems promising and did perform much better than the allograft without seeding (100% failure in 6 weeks). These grafts did not fare as well as the eight autografts, which demonstrated a 100% patency and competency rate at six weeks. There have been no clinical trials to date but this early experimental data are promising.

Clinically Available/Understudy

The following clinical studies involve the use of autogenous venous tissue but not *de novo* venous valves. It is my personal feeling that some of these approaches sprang for an intraoperative clinical need for a valve in a situation where preoperative investigations had suggested the presence of an autogenous valve but in reality there was none. The solution worked so well that the investigators found it a viable option in other patients devoid of the standard options.

Dr. Raju and associates have a small series of patients who received *de novo* valve reconstruction procedures.[21] These procedures involve the use of saphenous vein, a tributary of the saphenous vein, or the axillary vein for a donor vein tissue. Semilunar cusps are fashioned out of donor vein after trimming adventitia and part of the media, and the tissue is sutured into the recipient vein with the nonendothelial surface directed toward the lumen to decrease the risk of thrombosis.[21] Little experience has been gained with this method outside of the good clinical results reported in Dr. Raju's small series.

Another attempt to use autogenous vein as a valve substitute has been reported by Plagnol et al.[22] This approach invaginates a stump of the great saphenous vein into the femoral vein to fashion a bicuspid valve. Both experimental and clinical results have been reported.[22] They report 19 of 20 reconstructions to be patent and competent at a mean of 10 months. One valve demonstrated reflux because of insufficient valve size at the time of reconstruction. The invagination of an adventitial surface into the venous lumen is of some concern, not substantiated in this one report.

Most recently, a vascular surgeon from Italy has reported a series of bicuspid or monocusp venous valves made from dissecting the intimal/medial wall of the thickened postphlebitic vein to form cusps. The initial seven cases were reported in 2002 with acceptable preliminary results such that continued study was deemed appropriate.[23] A more robust report was given at the recent American Venous Forum meeting in February of 2005.[24] Eighteen venous valves were constructed in 16 patients with recurrent or nonhealing venous ulcers to treat chronic deep venous insufficiency due to the post-thrombotic process. The patients were anticoagulated for six months. Early thrombosis below the valve occurred in two patients and there was one late occlusion just after beginning oral contraceptive therapy. Therefore, 83.3% of treated segments remained primarily patent with significantly improved duplex and air plethysmographic results at a mean 22 months of follow-up. This technique certainly seems promising if others can duplicate these impressive results.

The Minimally Invasive Quest: Lessons Learned and Potentials

Our initial experience with a Z-type stent having a vein containing valve lining the entire lumen of the metal exoskeleton demonstrated that the addition of metal barbs to aid in securing the implant to the vein wall added trauma and security of position, but not necessarily patency.[13] Slight oversizing of the device appeared to be the best design for a stable positioning and for function. The configuration of the Z-stent allows for a moderate expansion in the area of the valve (see Figure 64.4) hopefully providing an area for valve sinus function that appears important to proper valve cleansing and considered essential for long-term function.[25] Rejection issues were not of concern since the tissue was an autogenous valve. No metal was exposed since the vein overlapped the ends of the metal stent prior to implant. However, the presence of the metal exoskeleton could lead to scarring (noted in the study) and therefore compliance problems over time.

Using a self-expanding stent (Wallstent, Schneider, Inc., USA) with autograft valve-bearing segment of vein secured within and utilizing overexpansion to hold the device in place, a one week animal study (n = 5) demonstrated residual nonocclusive thrombus attached to the exposed stent struts on the downstream end of the valve-stent in all animals.[26] The animals were anticoagulated for one week post implantation. The valve and vein were normal in appearance and function suggesting that the exposed metal was of concern as a site of thrombus formation. At six weeks, all valves (n = 6) were patent and five were competent by manual strip test. These valve-stents were now fully incorporated without thrombus. The one incompetent valve appeared to have been recanalized with multiple small channels present suggesting that the threat of thrombus is present until full incorporation making it desirable to minimize clot information as much as possible. Overall, the findings would suggest that the less exposed metal the better. If one views the histologic images, the vein wall is thickened with metal struts present within it. This would suggest that some compliant mismatch may develop yet not be demonstrated during this six-week study. However, the early animal results are promising. No clinical paper has been published with this valve/stent design to date.

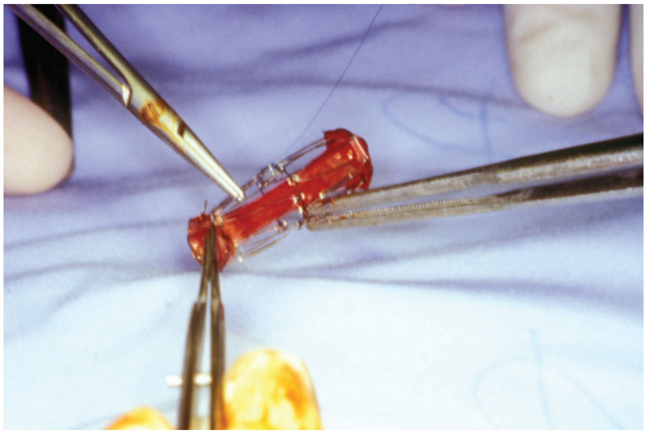


FIGURE 64.4 Our own method of attaching a vein containing valve to a self expanding Z-stent overlaps the vein over the ends of the metal exoskeleton thus eliminating exposed metal as a potential site for thrombosis. Also note that the Z-stent expands somewhat more widely in its mid-section (due to the restrictive nature of the attached vein circumference) to allow for sinus expansion if needed; however, scarring may prevent this motion over time.

Using a balloon expandable stent arrangement with a more challenging glutaraldehyde xenograft valve mounted within preformed quite poorly demonstrating all six inferior vena cava implants occluded at two months with collateral circulation present.[27] One cannot be sure whether the presence of xenograft material, the bulk of metal present, or possibly the trauma of balloon expansion either to the recipient vein wall or the donor valve was a factor in the poor results. Likely each factor contributed to some degree, and this particular valve/stent arrangement is unlikely to be the focus of investigation in the near future.

Percutaneous valve designs reaching clinical trials have demonstrated another observation of importance: less is better. As mentioned earlier, the glutaraldehyde preserved xenograft that had reached clinical trial was being continually redesigned to decrease the bulk of xenograft present and to streamline the device. The optimal design was never reached. The current Portland (or SIS) valve uses minimal metallic exoskeleton, when compared to the previously mentioned investigations, with promising results.[15] However, a design change was done to aid in proper centering of the valve, resulting in an increase in the exposed metal components but with still good animal experimental results.[17] A finding of cusp thickening necessitated a lengthening of the valve cusps for improved hemodynamics. One will have to see if the addition of increasing xenograft material will be an asset or disadvantageous as others have found with the presence of increasing foreign material.

The field of endovascular treatment for CDVVI is in its infancy. All that can be stated to date is that the concept is quite intriguing but much work is yet required for even a cursory understanding of the many facets involved with this approach.

CONCLUSIONS

A valve made of autogenous vein and surgically positioned into the lower leg venous system is currently the only artificial venous valve available with at least preliminary data to support its utility in the treatment of patients with end-stage CDVVI. There are potential nonautogenous

off-the-shelf venous valve substitutes that reside in research and development but lack clinical studies to support the transition to standard surgical use. All nonautogenous artificial venous valves to reach full clinical investigation have failed in early or mid-term analysis. The quest for a percutaneous option is just beginning to be investigated, but early study would suggest that minimizing nonautogenous tissue and exposed metallic components is best.

No option presented in this review can substitute for a good autogenous venous valve in the treatment of chronic deep venous valvular incompetence. However, the quest continues for those unfortunate individuals who require surgery but have no current option available to them.

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C H A P T E R

65

Post-Thrombotic Syndrome: Clinical Features, Pathology, and Treatment

SESHADRI RAJU

Postthrombotic syndrome (PTS) is a frequent sequel to deep venous thrombosis (DVT). Awareness of this long-term debilitating complication is low among treating physicians whose main focus is the acute embolic complications of DVT. PTS may take years and even decades to fully evolve when the patient is no longer in the care of the original treating physician.[1] Recurrent DVT that may occur years later after the initial event is a known risk factor for the development of PTS.[1] Serial follow up of patients after onset of DVT has provided important new perspectives on many aspects of PTS. After a bout of DVT, only a third of the patients are asymptomatic long term; but the other two thirds have PTS, half of them severe.[2] The direct and indirect costs of this disease that affects all adult age groups is estimated to be enormous, arousing the interest of public health planners.

CLINICAL FEATURES

Major symptoms are limb pain, swelling, and stasis skin changes including ulceration. Recurrent thrombophlebitis and recurrent cellulitis, the latter related to underlying tissue edema, are less well known and less frequent features. Symptoms are present in varying combinations and severity in individual patients. Pain is an important but variable component of the symptom complex. Limb swelling may be described by the patient as severe because it is painful even though only mild pitting is evident on examination. Some patients may not even be aware of limb edema evident to the examiner because it is pain free. Pain is absent in about 20% of patients. In about 10% of patients, pain may be the only symptom without other signs; a diagnosis of PTS may altogether be missed, because the limb looks normal. Severity of pain present may be exaggerated or understated by the patient due to individual variations in pain tolerance and other socioeconomic factors such as work situation; daily or frequent use of nonsteroidal or narcotic dependency for pain relief may not be readily disclosed unless specifically quetioned. Other essential elements of history may not be readily forthcoming as well. For example, previous DVT or severe trauma to the limb may not be volunteered because the remote event years ago had been forgotten or not considered relevant to current complaints. Because of these variables, a detailed comprehensive history-taking with leading questions is essential for proper assessment; clinical features detected on examination should be recorded and graded for severity during initial and follow-up visits for proper assessment of outcome. All components of relevant history and physical examination preloaded on a handheld device is a useful guide to those who see these patients only infrequently. The CEAP classification[3] and Venous Severity Scoring endorsed by the vascular societies can serve as readily usable templates for this purpose. In our own system, we have made some additional enhancements that we find useful. Pain is measured on a visual analogue scale,[5] a simple reliable measure of pain that can be used for outcome assessment as well. Limb swelling is variable throughout the day; limb measurement of swelling should be carried out at the same time of the day to be valid for follow-up assessment. Quality of life (QOL) measurements provide a view of outcome from the patient's perspective. The degree of disability and social constraint imposed by this disease can be surprising. Many QOL forms (e.g., CIVIQ)[6] are brief enough for routine use.

DIFFERENTIAL DIAGNOSIS

A clinical diagnosis of chronic venous insufficiency is readily apparent from history and physical examination in most cases but other rarer causes with somewhat similar clinical features have to be borne in mind: Periarteritis nodosa, ruptured Baker's cyst, rheumatoid arthritis, gout, Marjolin's ulcer, arterio-venous malformations of the calf muscles, adverse drug reactions with limb pain and swelling, acanthoma nigricans, pyoderma, and numerous other dermatological and systemic conditions. As venous insufficiency is common, particularly among the elderly, mixed pathologies that aggravate venous symptoms do occur. Combined arterial/venous insufficiency is not uncommon in the elderly; attention to the arterial component first is usually recommended. Differentiating primary from PTS may not be easy and mixed presentations occur as the following discussion on pathology indicates. Differentiation cannot be made on clinical grounds alone as history and physical findings may be similar including the appearance and size of ulcers. About 30% of DVT are estimated to be silent. In others DVT following trauma or surgery is simply missed as symptoms are submerged by expected postoperative pain—a common occurrence following orthopedic procedures on the hip or knee or for treatment of fractures. Patients with deep valvular insufficiency whether primary or post-thrombotic not infrequently present with new onset of acute calf pain and increased swelling in the context of ongoing chronic symptoms. In some, new or recurrent thrombosis is found. In others, no new thrombus is found; the symptoms are presumably due to decompensation of the calf pump from minor injury, low grade cellulitis or other obscure insult that disturbs the equilibrium of the calf pump. A diagnosis of PTS vs primary venous insufficiency is academic from the surgical viewpoint as the approach is the same regardless. But a diagnosis of PTS may have implications for long-term anticoagulation. In many cases, further investigations may provide helpful clarification.

PATHOLOGY

Our current view of PTS pathology is strongly influenced by the work of Strandness and colleagues.[7–10] Before then, post-thrombotic clinical syndrome had been viewed as primarily related to the development of reflux. In a remarkable series of landmark papers, these authors showed that the dominant pathology was a combination of obstruction and reflux even though isolated obstruction and reflux occurred in some. The location and progression of post-thrombotic reflux followed by serial duplex were unexpected and intriguing. Reflux occurred not only in segments involved by thrombus but also in segments remote from them. Reflux occurred and progressed over time not only in deep venous segments distal to the thrombotic segment but also in segments proximal; in the distal segments, dilatation of the valve station due to cephalad obstruction was *not* found to be the cause of reflux. The fact that reflux occurs and progresses over time in superficial as well as deep valves proximal to the obstructed segment suggests a different (maybe cytokines), as yet poorly understood, mechanism.

Some patients present with femoral valve reflux and thrombosis in the distal femoral popliteal segment or even the calf. This clinical profile could be due to reflux stasis–induced distal thrombosis. Repair of the valve reflux can abate recurrent thrombosis. Similar type of clinical presentation also can result from evolution of *de novo* reflux above the thrombotic segment as described by Strandness and colleagues. Perivenous and mural fibrosis is a feature of these valves with constriction and foreshortening of the valve station (see Figure 65.1). The valve cusps themselves are redundant and reflexive apparently as a result of the fibrotic wall changes. The fibrotic valve station is somewhat smaller than the classic primary valve, but the cusps themselves appear normal but redundant and can be repaired like the

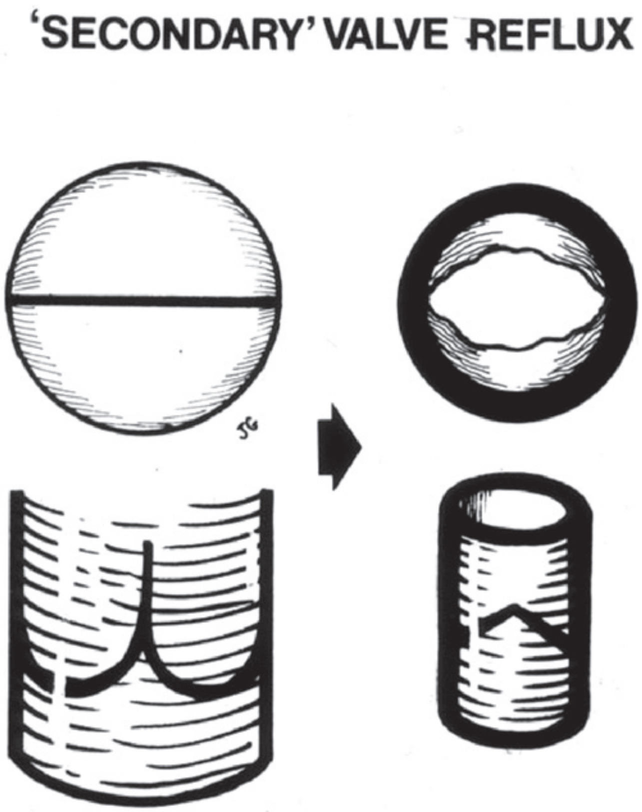


FIGURE 65.1 A possible mechanism for the production of valve redundancy and reflux in post-thrombotic valve stations. Valve station fibrosis may lead to luminal constriction resulting in secondary valve leaflet redundancy and reflux. Foreshortening of the valve station may lead to widening of the commissural valve angle, contributing further to development of reflux. (By permission, Annals of Surgery.)

primary valve using direct repair techniques. A plausible explanation for these features and perhaps for the remote reflux described by Strandness's group is that perivenous and mural fibrosis may extend beyond the thrombosed segment to involve adjacent segments of preserving valve cusps, but inducing secondary reflux from valve station restriction.[11] Valves may also escape destruction because the thrombus in the resident segment lyses, but not without inducing fibrotic changes as described.

INVESTIGATIONS

A comprehensive set of investigations are necessary for proper management of patients, particularly if invasive or other surgical intervention is contemplated. The aim is to clarify the pathology, identify the sites and nature of pathology, and grade its severity.

Duplex

Duplex is the initial and in many centers the only technique used. It has many deficiencies when used alone in assessment. As a qualitative tool, it can detect local reflux but cannot grade it nor can it adequately provide a measure of the overall severity of reflux in the limb when multiple segments are involved. Valve closure time (VCT) has received much attention as a quantitative tool in this regard. Though it can identify reflux in a particular segment, VCT has poor correlation with the severity of reflux present. Trivial reflux may be associated with prolonged VCT and conversely high grade reflux may have only slightly prolonged VCT. Peak reflux velocity has a better correlation, but not to a degree that is clinically useable.[12] At present relatively crude indices such as multisegment score (number of refluxive segments) or the presence of axial reflux are the best measures available. Iliac vein outflow obstruction, an important contributor to PTS,[13] is frequently impervious to duplex.

Venography

Unlike duplex, ascending venography provides a more composite view of venous pathology below the inguinal ligament. Post-thrombotic changes, segmental occlusions, and collateral patterns are readily apparent. The profunda femoris vein is the major natural collateral pathway in femoral stenoses and occlusions. This has an embryologic basis as the profunda femoris is the early axial vein receding to the mature pattern later in embryologic development. A putative profunda-popliteal connection apparently exists as a high resistance embryologic residue; profunda collateral flow can be observed as early as a few hours after onset of acute DVT in venograms. In chronic femoral vein occlusions, the profunda enlarges to the same caliber as the normal femoral vein (see Figure 65.2). This pattern of complete axial transformation of the profunda femoris vein[14] occurs in about 15% of postthrombotic limbs. Reflux may result from enlargement of the profunda valve station and may be severe with symptoms. Lesser degrees of profunda enlargement can be found in other cases where the femoral vein is not totally occluded but is stenotic.

Because the direction of collateral flow in the profunda is the same as natural flow direction in the vessel, it is very efficient. Once fully developed, the profunda fully compensates for the loss of femoral flow with few residual clinical symptoms from outflow obstruction. In iliac vein occlusions, collateral flow is mainly through tributaries of the iliac vein itself, requiring reversal of normal flow direction. Collateral flow seems to be less efficient and residual outflow obstruction is present in nearly half the cases with iliac occlusions.[15] These differential patterns of collateral development and function have clinical import. In patients with symptoms of outflow obstruction, iliac vein pathology is likely to be the culprit even if associated femoral vein occlusion is more readily seen on ascending venography. Ascending venography is inadequate for assessment of the iliac vein

FIGURE 65.2 Axial transformation of profunda femoral vein through a large profunda-popliteal connection. The femoral vein is largely occluded with the distal end seen as a stump. (By permission, Surgery.)

and the vena cava due to contrast dilution; stenotic lesions may easily be missed.

Transfemoral venography is the procedure of choice for pelvic venous assessment. Exercise femoral venous pressures[16] can be concurrently measured, which can be helpful in grading severity of outflow obstruction. Descending venography can also be performed at the same time to define the architecture of femoral valves. Descending venography is no longer used for grading reflux due to lack of specificity.

A common pattern in severely post-thrombotic limbs is where the entire outflow appears to occur through the superficial veins with nonvisualization of deep veins giving the appearance of wiped-out deep system.[17] This is invariably an artifact of technique. In most such cases a patent but post-thrombotic deep system with numerous collateral elements can be demonstrated on descending venography (see Figure 65.3). Presumably, there is a positive gradient across superficial to deep venous connections in these cases that contrast flow preferentially is restricted to the superficial system. The collateral contribution of the superficial system in such cases is negligible.[13,18] Since the deep system is patent, reconstructive procedures can be planned despite the spurious appearance on ascending venography.

FIGURE 65.3 Ascending venogram opacifies only superficial network (right). The deep system appears wiped out. This is often a technical artifact (see text); ample deep venous elements are demonstrated on descending venography (left).

Several authors beginning with Rokitanski[19] have documented the development of a dense perivenous sheath in postthrombotic iliac veins. This prevents or retards the development of collaterals. Surgical attempts have been made to remove the sheath for improving flow. The venographic appearance in such cases is one of diffuse stenosis without collaterals. Iliac vein pathology is easily missed in such cases, especially with ascending venography. With transfemoral venography, the diffuse lesion can be quite evident or subtle requiring measurements of vein diameter, which is seldom practiced. Because of this and other factors cited earlier, the sensitivity of venography in iliac vein pathology is only in the order of 60%.[16,20]

Intravascular Ultrasound (IVUS)

Intravascular ultrasound is superior to venography in the assessment of post-thrombotic iliac vein and the inferior vena cava.[20] Perivenous and mural fibrosis, stenoses and trabeculae are readily seen. It is invaluable in iliac vein stent placement, a subject treated at greater detail in Chapter 60.

Lymphangiography

About 30% of patients with deep venous insufficiency have lymphographic abnormalities such as pooling and delayed or absent lymphatic transport.[21,22] Most are thought to be secondary to venous pathology from lymphatic exhaustion or damage. Some may be reversible with correction of venous pathology.[21] Lymphographic information has prognostic value in resolution of leg swelling and affected patients may be adequately forewarned before interventions.

Airplethysmography (APG)

Measurement of ejection fraction and residual volume have been suggested as indirect indices of outflow obstruction. In our own and others' experience, specificity and sensitivity have been inconsistent. VFI_{90} appears to be a useful measure of reflux.[23]

Ambulatory Venous Pressure Measurement

Ambulatory venous pressure measurement provides a global index of venous function in the limb encompassing multiple components.[24] Post-exercise pressure (% drop) has an inconsistent relationship to the severity of outflow obstruction[15] presumably because of the variability of calf pump efficiency. The recovery time or venous filling time (VFT) has been useful in assessing severity of post-thrombotic pathology and reflux.[17] A postoperative VFT of

>5 seconds bodes well for a good surgical outcome; a VFT of <5 seconds the opposite. The mean improvement in VFT after successful repairs with good clinical outcome is generally in the order of about 6 ± 4 (SD) seconds. After successful valve repair, postoperative VFT does not reach normal levels in many patients. VFT is influenced not only by reflux but a multiplicity of other factors.[24] Compliance of the conduit below the valve profoundly affects VFT even more than reflux at the valve.[25] Failure to normalize or substantially improve VFT is probably related to the poor venous compliance in post-thrombotic extremities.

Measurement of Outflow Obstruction

Reduced or absent phasicity on duplex examination is often indicative of outflow obstruction at the iliac vein level,[15] the information being qualitative. There are no reliable methods of functionally quantifying and grading outflow obstruction at the present time. Plethysmographic outflow fraction measurement such as with strain gauge technique and APG yield unacceptably high false positives[13] due to compliance changes in the post-thrombotic calf; a reduced outflow fraction (<50%) results from subpar emptying of the venous pool from poor compliance as often as from outflow obstruction per se. And poor compliance may be present without obstruction. A reduced outflow fraction is indicative of post-thrombotic changes, not necessarily obstruction.[26] Pressure-based tests to detect and grade severity of obstruction such as arm/foot venous pressure differential with reactive hyperemia, exercise femoral venous pressures measurement, and intraoperative femoral vein pressure measurement with papavarine are positive only in about a third of cases.[20] Assessment of outflow obstruction currently rests entirely on morphologic methodology (IVUS) restricted to the iliac vein segment.

TREATMENT

Compression Therapy

Compression therapy is the oldest and until recently the only therapeutic option available to treat PTS. It has been reported anecdotally to be ineffective in PTS but no systematic study has been undertaken. Compression therapy remains the initial approach in chronic venous disease including PTS. Some patients do fail compression therapy despite faithful compliance. Noncompliance, however, is the major cause of compression failure and recurrent symptoms.[27–29] Noncompliance is high even in cold climates as documented in several community surveys. Long-term supervision or monitoring by health care workers has been advocated to improve compliance. However, noncompliance is high even under supervision.[29,30] The reasons for noncompliance are many—tightness or fit (cutting off circulation), warm weather, lack of efficacy, contact dermatitis, recurrent cost and inability to apply stockings due to frailty or arthritis are among the many reasons/excuses cited by patients. But the main underlying reason, often unstated, appears to be the restrictions and negatives of compression regimens in today's image–conscious world with expectations of an unrestricted lifestyle. Thus compression is a quality of life issue from the patient's viewpoint. Demands for compliance are unlikely to succeed after previous entreaties have failed and may not be appropriate when therapeutic alternatives have become available. Compression should be viewed not as an end itself, but complementary to the extent patients are willing to use them. Compression should be considered a failure regardless of the cause including noncompliance if symptom relief is not obtained after trial over a reasonable period of time, say three to six months depending on the clinical and socioeconomic situation of the patient. Worsening of symptoms or onset of complications such as recurrent infections during the trial period are also considered failures. Some patients are not candidates for compression therapy at all due to comorbidities (e.g., arthritis, frailty, or arterial compromise)[31] or special work situations. Nonresponders should be offered alternatives, not life-long unna boot regimens as was the case before by necessity, and continues to be so in many parts of the world due to a conservative philosophy of health care delivery.

Saphenous Vein Ablation

There has been traditional advice against saphenous ablation in the presence of deep venous obstruction (secondary varices) to preserve its collateral contribution. The collateral contribution of saphenous vein in the presence of deep venous obstruction is insignificant.[13,18] Stripping of a refluxive saphenous vein in PTS cases can provide significant symptom benefit by eliminating the reflux component without jeopardizing the limb.[18] Stripping can be easily combined with valve reconstruction in the femoral area. The newer minimally invasive techniques of saphenous ablation are suitable alternatives as well and are easily combined with iliac vein stent placement when indicated (see later).

Valvuloplasty

In PTS patients, direct femoral or popliteal valve repair can be performed if the basic valve architecture is preserved. Eriksson stressed the importance of profunda valve repair in post-thrombotic cases due to the frequent presence of collateral reflux.[32] We prefer an external or transmural technique without a venotomy for these cases as they are faster and hence multiple repairs (i.e., femoral and profunda) can be performed in a single sitting; and repairs can be carried

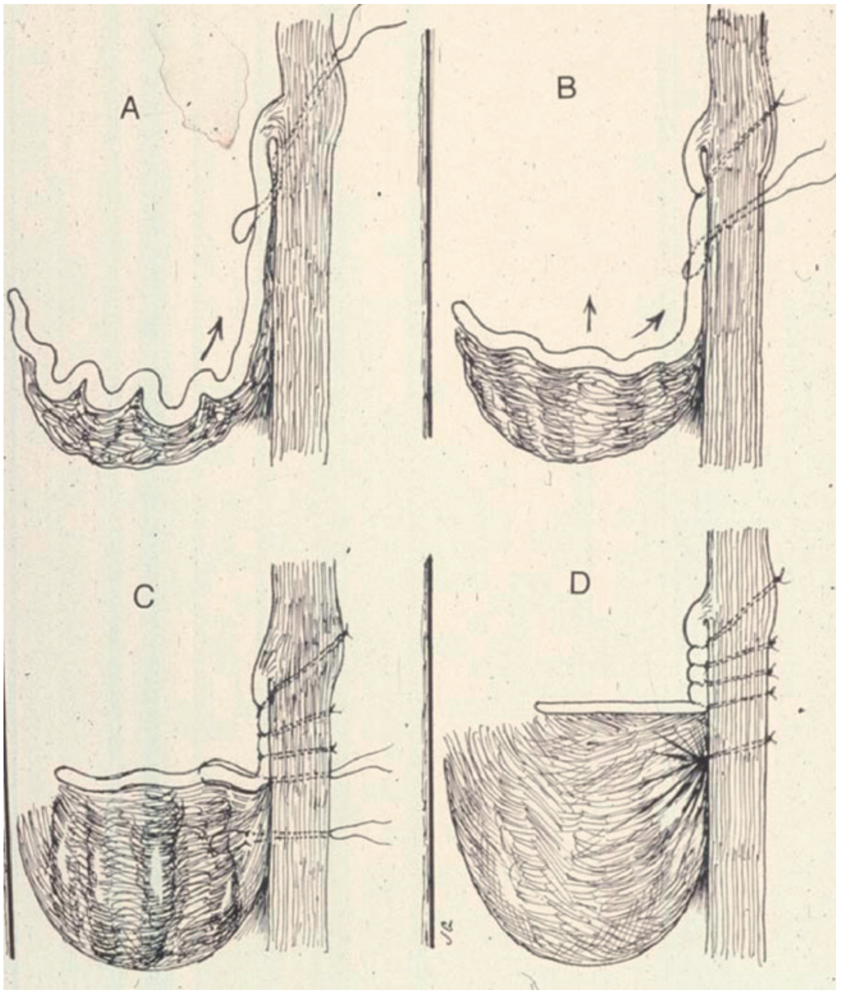
out even in constricted or small valve stations. The internal technique is disadvantaged in comparison.

Our own preference is trancommissural technique,[33] which closes the wide valve angle present at the commissure and simultaneously tightens the lax valve cusps by transmural sutures that can be placed blindly in a reliable fashion (see Figure 65.4). The first step in the procedure is to carry out an adventitial dissection to peel away the fibrous sheath surrounding the valve station. Valve attachment lines should become visible after the dissection. They should be defined in their entirety, which is necessary for placement of transcommissural sutures. Though the sutures are placed blindly, adherence to the technique as described in the original publication will result in technical success of >95%.

Absent or interrupted valve attachment lines invariably indicate cusp dissolution or damage beyond direct repair. In such cases one should proceed forthwith with axillary vein transfer without wasting time on performing a venotomy in a futile search for repairable valve cusps.

Axillary Vein Transfer

Axillary vein transfer[34] is the mainstay of repair in PTS cases when direct valve repair is not feasible due to damage to the valve cusps. Seemingly a simple technique, it is in



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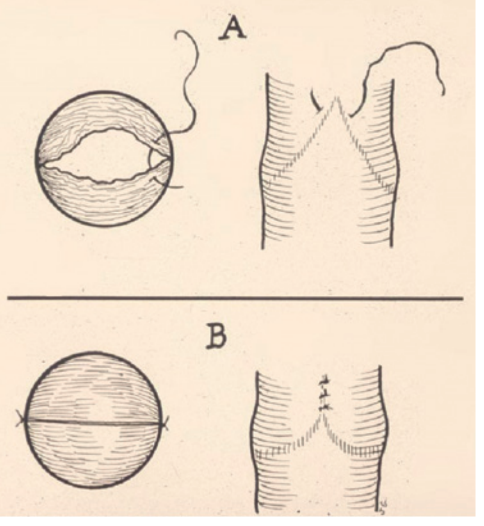


B

FIGURE 65.4 **A**. The initial through-and-through oblique transluminal suture placed at commissural apex catches sagging leaflets and resuspends them, **A** to **D**. Transluminal sutures with each successive suture biting deeper and less oblique than suture above to pull up and, tighten cusp edge, deepen sinus, and appose valve attachment lines. Each suture is tied before the next is placed. One or two of the most caudally placed sutures may actually pass through body of leaflet rather than edge, with no subsequent ill effects. **B**. Correct suture placement narrows the angle between valve attachment lines and tightens cusps, resulting in good apposition. (By permission, J Vasc Surg.)

fact, quite demanding, requiring precise execution. Proctored learning is recommended to achieve consistently good results. The transferred valve should match the size of the native valve station being reconstructed. In most cases, the axillary vein is the preferred donor site to obtain a good size match. In a minority, the proximal brachial vein may also be suitable in size. We approach the axillary-brachial veins through a transverse incision in the armpit along the skin crease; exposure of 5 to 6 cm length of axillary vein segment will require ligation and division of three or more tributaries in the area. One or more valves will then come into view. We have not found preoperative duplex examination useful in locating a transferable valve. The valve with a good size match is chosen for transfer. A valve high up in the axilla at or near the first rib is consistently present and is the largest. This may require additional dissection for exposure. The chosen valve is then tested for competence by negative (emptying the infravalvular segment) and positive (squeezing the supravalvular segment) strip tests. About 40% of axillary valves will fail the strip tests, in which case they should be repaired by the transcommissural technique preferably *in situ* or on the bench before transfer. A 4 cm vein segment housing the valve is excised and the ends of the remaining vein ligated. A lesser length will interfere with later anastamoses as the excised segment shrinks, risking the valve cusps being caught up in the suture lines. Reconstruction of the donor vein is not required; outflow obstructive symptoms in the donor limb are extremely rare. The transferable valve is dropped in cold balanced salt solution for a few minutes and then transferred to the recipient site. A 1 cm segment of the recipient vein is excised, which results in retraction of the cut ends leaving a longer gap. The axillary valve is transferred in proper orientation and the proximal anastamosis is performed first. Interrupted 6° monofilament permanent sutures should be used throughout. Continuous sutures, howsoever expertly applied, will result in postoperative suture line stenosis as the native and transferred vein segments dilate to their normal caliber, freed of intraoperative spasm. Once the upper anastamosis is completed, the valve should be retested for competence by the strip tests. Some axillary valve sinuses are shallow and are prone to *de novo* reflux with minor distortions of architecture that may occur during the transfer procedure. A transcommissural repair may then be required at this stage to achieve perfect competence. Before starting the distal anastamosis, the distal end of the recipient vein should be trimmed to match the length of the donor segment put on a mild stretch. A slack or overstretched donor segment will result in reflux. Proper rotational orientation of the transferred segment is crucial. There should be no hesitancy to take down and redo the distal suture line if imperfections or reflux is discovered after completion. Final positive and negative strip tests are performed to assure competence. The axillary vein has a thinner muscle layer than the native recipient vein because of the higher orthostatic pressures prevalent in the latter. This may result in gradual dilatation of the transferred axillary vein segment with onset of reflux. This problem encountered in early experience was addressed by placing a prosthetic sleeve around the transferred vein segment. Currently an 8 to 10 mm PTFE sleeve, 3 cm long, is split open and sutured back as a loose fitting sleeve around the transferred axillary valve with one or two anchoring sutures to the adventitia to prevent migration. Slipping an unopened sleeve over the lower end of the transferred segment before beginning the distal suture line may obscure rotational orientation of the transferred valve resulting in reflux after completion of the suture line and is to be avoided. The incision is closed with a closed drainage system. Penrose drainage is provided for the axillary incision. To avoid compression of the repair by fluid collection in a tight space, only the superficial fascia is closed with interrupted sutures and the deep fascia is left open.

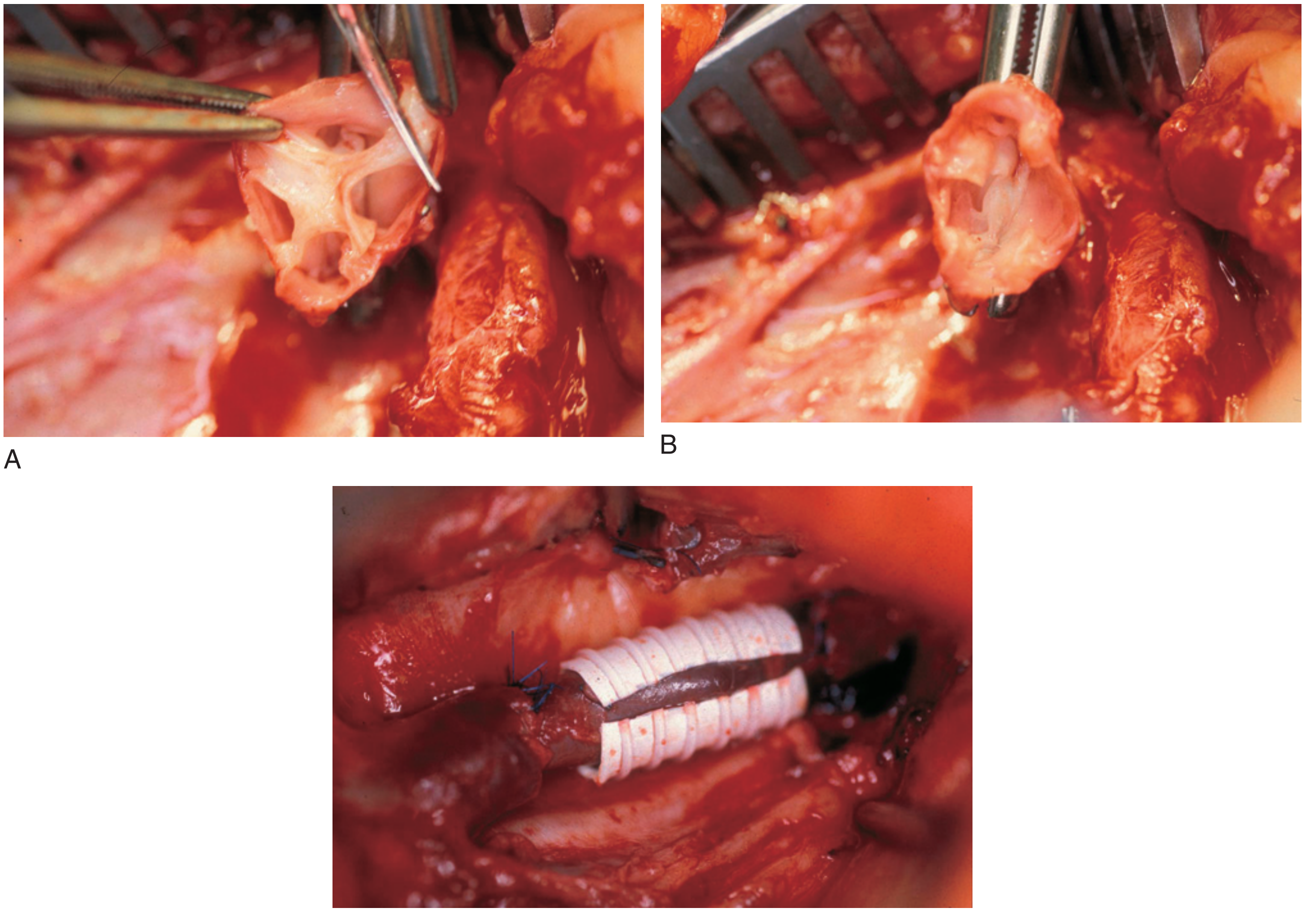
In trabeculated post-thrombotic veins, modifications of the basic technique are necessary. The trabeculae at the site of proximal and distal suture lines are excised (see Figure 65.5A,B,C) to create a single lumen at the site for anastamoses.

In a subset of PTS patients both the femoral and profunda femoral veins are severely post-thrombotic with destroyed valve structures. The femoral confluence can be repaired with individual axillary vein transfers or by en bloc transfer of basilic-brachial confluence provided valves are present and size match requirements are satisfied (see Figure 65.6).

Postoperative Care after Valve Reconstruction

Hematomas and seromas occur in about 10% of cases because of anticoagulation. They should be promptly evacuated to avoid compression and thrombosis of the repair.

Low molecular weight heparins are used at prophylactic dosage starting before surgery and continuing until warfarin anticoagulation started on the first postoperative day achieves therapeutic range. Intraoperative and postoperative pneumatic compression is routine. Warfarin anticoagulation is maintained at therapeutic levels for at least six weeks, by which time operative endothelial injury is fully healed.[35] Long-term anticoagulation is determined on an individual basis. Thrombophilia, two or more episodes of prior thrombosis, or severe diffuse post-thrombotic damages with little functional reserve (ambulatory venous pressure) is an indication for chronic anticoagulation. In others, low-dose warfarin regimen may suffice to eliminate the inconvenience of frequent INR monitoring and to reduce the risks of chronic



A B C

FIGURE 65.5 Technique in trabeculated veins. Trabeculae are excised (**A**) to create a single lumen (**B**) for axillary vein transfer (**C**).

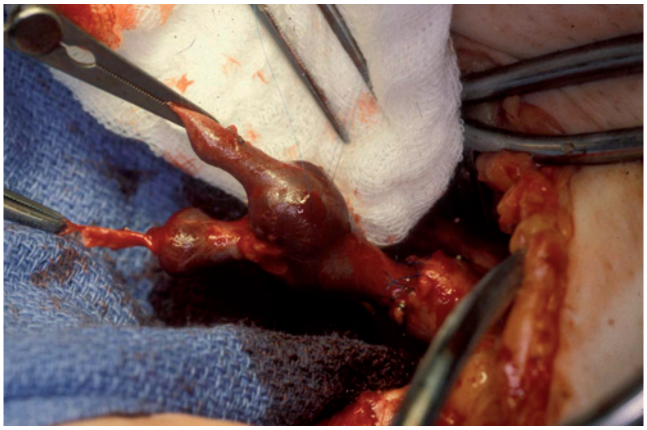


FIGURE 65.6 Reconstruction of the femoral confluence using axillary-brachial-basilic complex. Proximal clamp is off after completion of the proximal suture line. The brachial valve is competent. Refluxive (de novo) basilic valve is being repaired by transcommissural technique.

full dose anticoagulation. Warfarin-induced impotence is a consideration in younger male patients.

Surgical Results

In our own experience, recurrence–free ulcer healing in PTS cases at five years was ±60%, not different from primary valve repairs.[36] There was also no difference between the various techniques whether internal, external, or axillary vein transfer. Results with the transcommissural technique have been similar.[33] Results of axillary vein transfer in over 100 trabeculated veins were particularly surprising (see Figure 65.7).[17] Cumulative long term patency and recurrence-free ulcer healing at 10 years were 83% and >60%, respectively, not different from axillary vein transfer results in a matched group of PTS limbs without trabeculated veins. Perrin reported clinical results very similar to these in a large group of post-thrombotic cases followed over five years.[37] He also noted a post-operative thrombosis rate of 32% in PTS cases using intense surveillance with

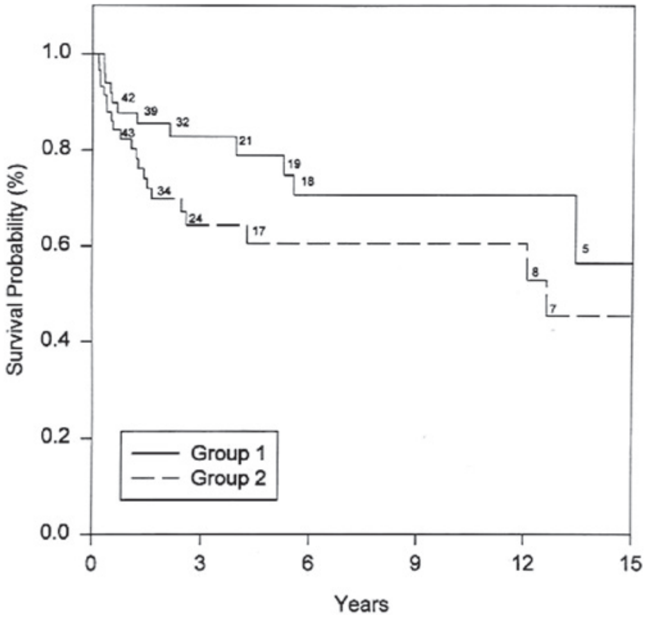


FIGURE 65.7 Actuarial recurrence-free ulcer healing in the subset of patients with stasis ulceration after axillary vein transfer to nontrabeculatcd (Group 1) and trabeculated veins (Group 2). (By permission, J Vasc Surg.)

postoperative venography. Many were localized partial thrombi and most had recanalized later. He did notice a significant difference between PTS and primary cases in ulcer healing (60% and 75%, respectively, at five years) attributing the difference to the post-operative thromboses. Masuda and Kistner reported long-term results of valve reconstruction in primary as well as a subset of proximal primary reflux with distal thrombosis, presumed secondary to proximal reflux.[38] Internal valvuloplasty or vein segment transfer (end to side anastamosis of the femoral vein to the profunda femoris below the profunda valve) were largely used in the PTS subset. PTS results were inferior (43% cumulative) to valve repairs in primary cases (73% cumulative) at 10 years. It is not clear if these different results are due to choice of technique (i.e., Segment transfer) or other specifics of the PTS subset.

Iliac Vein Stent Placement in PTS Reflux

Iliac vein stent placement recently has emerged as effective therapy in PTS.[39] A surprising initial finding was relief of symptoms including healing of stasis ulceration (55% cumulative near term) with stent placement alone even when the associated reflux remained uncorrected.[40] These unexpected results appear to have been sustained over a longer follow up of >4 years as well (unpublished data). This has important implications for the management of PTS as the majority have combined obstruction/reflux.[10,13,39] Most patients should benefit from stent placement alone, a minimally invasive outpatient procedure. Open valve reconstruction procedures will be required only in recalcitrant cases that have failed initial stent placement; later valve reconstruction in case of stent failure is not precluded.

CONCLUSIONS

There is reluctance to undertake valve construction in general, and particularly in post-thrombotic cases for fear of thromboembolic complications. Certainly the venographic appearance can be daunting in many PTS cases with trabeculated veins. However, thromboembolic complications have been surprisingly infrequent in our own experience,[11,14,17,33,34,36] with the protocol described. Furthermore long-term patency has been excellent suggesting that trabeculated veins have become resistant to further insults including surgical trauma. Recent favorable experience with open endovenectomy in trabeculated veins[41] fortifies this impression. Though reported results in some series appear to have been inferior in PTS cases compared to primary cases, overall PTS results are still encouraging when viewed as salvage in patients with no other viable therapeutic options. Considering the current large pool of patients who have failed compression therapy, the potential benefits of an aggressive approach to this debilitating problem are obvious. The advent of stent technology is a hopeful development. Iliac vein stent placement is the initial procedure of choice in PTS cases. Valve reconstruction will be required only in the smaller subset that fail initial stent placement. Valve reconstruction should be offered to this subset as an available option.

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